A STUDY OF LIPID PROFILE ABNORMALITIES IN RHEUMATOID ARTHRITIS

DISSERTATION

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CERTIFICATE

This is to certify that this dissertation entitled **THE LIPID PROFILE ABNORMALITIES IN RHEUMATOID ARTHRITIS"** submitted by **Dr.L.A.RAVI.** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2009 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled "**A STUDY OF LIPID PROFILE ABNORMALITIES IN RHEUMATOID ARTHRITIS"** is done by me at Madras Medical College & Govt. General Hospital, Chennai during January 2008- September2008 under the guidance and supervision of **Prof.M.JUBILEE, M.D.**

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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CONTENTS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction[1] RA causes significant morbidity as a result of synovial inflammation, joint destruction and associated disability [2]. Epidemiological studies have shown an increased premature mortality in patients with RA compared with the general population[3-7]. Several investigators reported an excess of cardiovascular morbidity and mortality among RA patients[62,-65].

Though rheumatoid vasculitis in severe RA cases with high rheumatoid factor titres occasionally causes acute myocardial infarction the overwhelming majority of cardiovascular deaths in RA result from accelerated atherosclerosis[2,8,9].

Risk factors for atherosclerotic events and cardiovascular disease include male sex, increased age, elevated plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), high blood pressure, smoking and diabetes mellitus[10-13]. Approximately 50% of atherosclerotic coronary artery disease (CAD) in the community occurs in the absence of traditional risk factors[14].

In general, and with some variations between different studies, the lipid profile of patients with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C whereas contrasting results have been published on the serum levels of TC and LDL-C[15-20]. Importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio[15]. This ratio represents an atherogenic index, which is an important prognostic marker for cardiovascular disease[15]. Indeed, the risk of myocardial infarction increases considerably when this ratio is higher than five, and it should ideally be four or less[15,16].

There are few studies in India about lipid profile abnormality in Rheumatoid arthritis and inflammatory activity altering lipid profile in RA patients.There is lacuna of knowledge about this aspect of disease in Indian patient.This study aims to address this issue.

AIMS OF THE STUDY

1. To study the Lipid profile abnormalities in Rheumatoid arthritis patients.

2. To assess the correlation between Lipid abnormalities and severity of the disease.

3. To assess the role of Lipid abnormalities in the development of cardiovascular disease in Rheumatoid arthritis.

HISTORICAL REVIEW:

The rheumatic disease have been recognized since the fifth century before Christ under the title of **"ARTHRITIS" (COPEMAN 1969**) .The rheumatism was probably introduced by Galen in medieval times to designate pain caused by one of four humours[21].

The first descriptionofthedisease is usually attributed to **LANDRE-BEAUVAIS (1800)** who published his observations as a thesis **SAIVEGES (1763)** had previously written about a secondary type of arthritis which might follow acute rheumatisim . **Sir ALFRED BARRING GUARD** described RA and suggested that it was a different disease from gout (1859)[23].

STRAGEWAYS (1907) advanced our knowledge about the pathology of the disease. The theory of focal sepsis was introduced by **WILLIAM HARTER (1901)**.Rheumatoid factor was discovered by ross[23].

Shortly afterwards, the syndrome was described independently by **CHAUFFARD** in france and Juvenile RA is Still called chauffard still"s disease[21].

FERESTER (1930) suggested treatment with gold salt.[23] The discovery that the disease process could be reversed temporarily by cortisone was made by

HERCH and **KERDALL** for which they jointly received the novel price in 1950[23].

In 1953, **caplan** described the rheumatoid pneumoconiosis in coal workers who had a history of exposure to dust[23].

DEFINITION:

Rheumatoid Arthritis is defined as a chronic systemic inflammatory disorder characterized by deforming symmetrical polyarthritis of varying extent and severity, associated with synovitis of joints and tendon sheath, articular cartilage loss, erosion of juxta articular bone and in most patient the presence of IgM rheumatoid factor in the blood.[23]

EPIDEMIOLOGY:

*Incidence was 54/1 lakh in women

-24.5/1 lakh in men[23].

80% of all patients developing the disease between the ages of 35 and 50 years. However the incidence increased to a maximum in women over 45 years and men continued to raise into seventh decade.[30]

*prevalence of RA lies between 0.8 and 1.1 percent of adult population.

*Women are affected 3 times more often than men[23].

ETIOLOGY:

The initiating cause of rheumatoid arthritis remains unclear.

1. **Genetic factors :-**

Genetic studies of the distribution of RA in families and in mono & dizygotic twins show that there is a small but definite contribution of genetic factors to the disease.

In twins studies, there is around 30% concordance of disease in identical twins and around 5% in non-identical twins.

- 10% of patients with RA will have an affected first degree relatives.
- Recent studies have shown an association between HLA-DR, (HLA-DW4 and HLA-DW14) and seropositive disease. In Indians RA is most commonly associated with HLA-DR1.
- More specially , the disease susceptibility is associated with sharped epitope of specific aminoacid sequence on the beta-1 chain of a number of class II –alleles located in the third allelic hypervariable region of HLA-DR B1, between aminoacid residue 67 and 74 which flank the T-cell recognition site[23].

2.Environmental factors:

It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host.

- Organism included EBV , CMV , Parovirus B19[31], Rubella virus and mycoplasma.
- Cigarette smoking was associated with increased risk of RA.
- Exposure silica dust, organic solvent, mineral oils were associated with increased risk of RA.

3.Host factors.

- Exposure to oral contraceptive pills confers protection and postone the onset of RA.

-Pregnancy is associated with suppression of disease. The incidence of RA is increased following parturition and during laction[23].

-The incidence of disease is increased in old age male because of low testosterone[23].

PATHOLOGY:

1.Rheumatoid disease process in the joints is characterized by

a. Synovitis

b. Inflammatory effusion

c. Cellular exudates into the joint space

d. Damage to tendon, ligament and bone in and around articulating surfaces of the joint by the proliferating inflammatory tissue called pannus[26].

2. Extra articular features associated with RA consist of two types of lesion.

- First is fibrointimal hyperplasia without inflammatory changes leading to vascular occlusion.
- Second lead to extravascular lymphocyte macrophage granuloma lesion of RA[27].

3.Extravascular nodule formation in areas subject to pressure is characteristic granulomatous lesion of RA.

PATHOGENESIS

The inflammatory synovial membrane produces large amount of immunoglobulins mainly as RF. The cellular basis for production of RF is well established.

Lymphokines:

The inflammatory synovium contains activated T- lymphocyte, which produce lymphokines into the synovial fluid. These in turn

activate additional T-Lymphocytes, act as helper factors for B-cell proliferation, stimulate fibroblast to produce collagen and stimulate macrophage.

Activated macrophages produce prostaglandin E2 and enzyme such as collagenase, elastase and cathepsin, TNF which may play a part in destruction of bone and cartilage[28].

IL-1 and TNF have potent effects on synovial fibroblast and chondrocyte function that involve stimulation of prostaglandin and collangenase production as well as modulation of synthesis of proteoglycans, collagen and fibronectin.in organ culture both IL-1 and TNF cause cartilage cells to resorb matrix. IL-1 Can also act on osteoblast to generate osteoclast activation[28].

Rheumatoid factor:

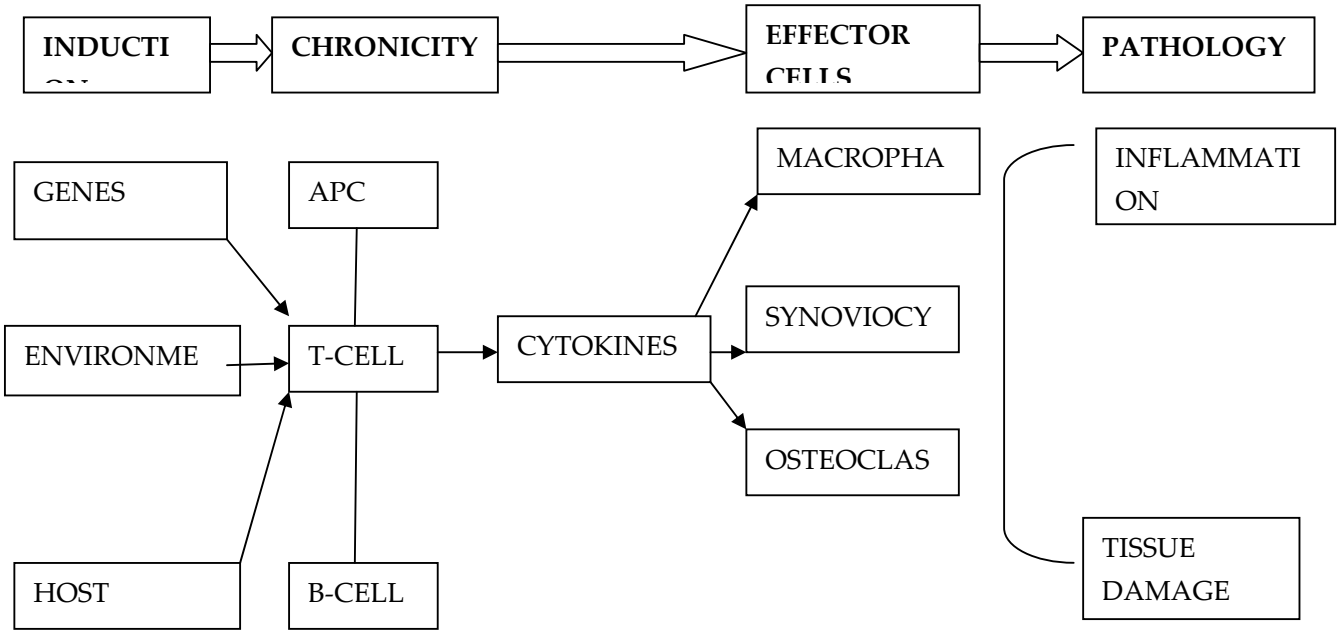
The immunological abnormalities in the serum of the patients include hypergammaglobulinemia and the presence of RF. IgG RF binds with its own Fc portion to form immune complex which are found in the synovial membrane and synovial fluid surrounding blood vessels.they are phagocytosed by neutrophils ,monocytes and

macrophages with release of number of enzymes and inflammatory mediators.

In addition to the above, immune complex activate complement cascade which generate inflammatory and chemotactic factors with futher accumulation of inflammatory cells.

High RF titre correlate with the presence of severe erosive joint disease, nodules ,vasculitis,and extra articular complication of RA[24].

SIMPLIFIED DIAGRAM OF FOUR STEPS IN THE AETIOPATHOGENESIS OF RA[23].



DIAGNOSIS

The American college of Rheumatology (ACR)[25] has developed and revised criteria for the classification of RA based on a hospital population of patients with established active disease. These criteria distinguish active RA from other forms of inflammatory arthritis with a diagnostic sensitivity and specificity of about 90%.

Table:1 1987 REVISED AMERICAN RHEUMATISM ASSOCIATION CRITERIA FOR CLASSIFICATION OF RHEUMATOID ARTHRITIS[25] *

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hr before maximal improvement
2. Arthritis of three or more joint areas	At least three joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician (the 14 possible joint areas are [right or left] PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
3. Arthritis of hand joints	At least one joint area swollen as above in wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as in criterion 2) on both sides of the body .
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum "rheumatoid factor" by any method that has been positive in less than 5 percent of normal control subjects
7. Radiographic changes	Changes typical of RA on PA hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

First Four criteria for atleast 6 weeks duration.RA is defined by presence of four or more criteria.

CLINICAL FEATURES

RA is a systemic disorder characterized by a chronic inflammatory synovitis mainly the Di- Arthrodial joint[34].

- Prevalence and onset
    - More common in female sex. Majority have insidious onset of illness(70%). Other modes are
        - Acute 15%
        - Oligo- articular 44%
        - Systemic 10%
        - Polyarticular 55%
        - Palindromic 5%
        - Monoarticular 21%

Articular Manifestations:

RA is typically a distal symmetrical small joint polyarthritis involing the PIP and MCP joints of the hands, wrist, MTP joints, ankles, knee and cervical spine.Any Synovial joint including cricoarytenoid joint, tissue such as bursae and tendon sheath are inflammed[55].

The most common symptoms are pain and stiffness.The latter frequently exhibit diurnal rhythms, worse on early morning. The affected joints worse as the disease advances, muscle atrophy , tendon sheath and joint destruction results in limitation of joint movement, joint instability , subluxation and deformity.

Characteristic deformity include flexion contracture of small joints of hands and feet, the knee, hips and elbow.Anterior subluxation of MCP joint is common with ulnar deviation of fingers .Others include swan neck deformity, Boutonniere deformity, plano key sign, carpel collapse and fusion, Z – deformity of thumb.

In the forefoot, subluxation of MTP joint is followed by clawing of toes and callosities.Involment of knee is a common cause of disability. Synovial effusion in posterior aspect leads of valve like mechanism and cyst formation and occasional ruptures.Tricompartmental articular damage leads to fixed flexion deformity,valgus deformity and total fusion[55].

Axial involvement of cervical spine occurs in 8% .atlantoaxial subluxation upto 25% of patients. Subaxial subluxation present as a series risk of cord compression[55].

- **Extra articular features[27]:**

1.Rheumatoid nodules:

The commonest non-articular manifestation of RA is the granulomatous nodule which is characteristically found on the extensor aspect of forearm, elbow, scalp,scapula, sacrum and achiles tendon. Ulcerations and secondary infections are common. This can also occur in pleura. Lung parenchyma, pericardium, vocal cord and heart valves. Nodules are associated with positive test for RF[27].

2. Vasculitis:
   - Reynaud's phenomenon can occur in the course of the disease.
   - Diffuse necrotizing vasculitis seen as nail fold infarcts, digital gangrene and purpura[27].
3. Pulmonary manifestations[55]:
   - Caplan syndrome consists of nodular opacities varying in size from 0.5 to 5 cm throughout both lungs in a patient with RA.

   Others are,
   - Pleurisy
   - Pleural effusion
   - Pneumothorax
   - Fibrosing alveolitis
   - Nodules and cavitation

- Bronchiectasis
- Obliterative bronchiolitis

4. Cardiovascular manifestations:
   - Pericarditis occurs in less than 5% of cases.
   - Very rarely heart block, cardiomyopathy, aortic regurgitation and coronary artey occlusion occurs.
5. Ocular features:
   - Keratoconjunctivitis sicca occurs in 10% of cases.
   - Episcleritis
   - Scleromalacia
   - Scleromalacia perforans
6. Neurological manifestations:
   - Entrapment neuropathy of median nerve, ulnar nerve, peroneal nerve, posterior tibial nerve
   - Peripheral neuropathy
   - Vasculitis may lead to mono neuritis multiplex
   - Atlanto axial subluxation leads to cervical cord compression
7. Musculo skeletal manifestation:
   - Osteoporosis, muscle weakness and wasting can occur adjacent to inflammed joints.
8. Lymphatics:

- Lymphadenopathy is usually found in nodes draining the inflammed joints. The nodes are discrete and non tender.

9. Renal:

Renal papillary necrosis and interstitial nephritis occur due to NSAID usage

Membranous glomerulo nephritis occur due to gold and d-penicillamine usage.

LIPID TRANSPORT AND METABOLISM.

The major lipids are relatively insoluble in aqueous solutions and do not circulate in the free form. Free fatty acids are bound to albumin, whereas cholesterol, triglycerides, and phospholipids are transported in the form of lipoprotein complexes. The complexes greatly increase the solubility of the lipids.

There are six families of lipoproteins , which are graded in size and lipid content. The density of these lipoproteins (and consequently the speed at which they sediment in the ultracentrifuge) is inversely proportionate to their lipid content. In general, the lipoproteins consist of a hydrophobic core of triglycerides and cholesteryl esters surrounded by phospholipids and protein

The way these lipoproteins are organized into an exogenous pathway, which transports lipids from the intestine to the liver, and an endogenous pathway, which transports lipids to and from the tissue[33].

The protein constituents of the lipoproteins are called apoproteins. The major apoproteins are called APO E, APO C, and APO B. There are two forms of APO B, a low-molecular-weight form called APO B-48, which is characteristic of the exogenous system and a high-molecular-weight form called APO B-100, which is characteristic of the endogenous system.

Table:2 Characteristics of major classes of lipoproteins in the plasma.

Lipoprotein	Diameter(mm)	Source	Major Lipids	Major apoproteins	Density
Chylomicrons	90 - 1000	Intestine	Dietary triglyceride	AI, AII , B48, CI, CII, CIII, E	<0.95
VLDL	30 - 90	Liver	Endogenous triglyceride	E, CI, CII, CIII, B100	0.95 to 1.006
IDL	25 - 30	VLDL	Cholesterol ester, triglyceride	E, CIII, B100	1.006 to 1.019
LDL	20 - 25	VLDL	Cholesterol esters	B100 ,	1.019 to 1.063
HDL	10 - 20	Liver, Intestine	Cholesterol esters	AI, AII	1.063 to 1.125

Chylomicrons are formed in the intestinal mucosa during the absorption of the products of fat digestion . They are very large lipoprotein complexes that enter the circulation via the lymphatic ducts. After meals, there are so many of. these particles in the blood that the plasma may have a milky appearance.

Table:3 ATP III[61] Classification of LDL, Total and HDL Cholesterol and Triglycerides (mg/dL)

Total cholesterol	
<200	Desirable
200 - 239	Borderline High
≥240	High
LDL cholesterol	
<100	Optimal
100 - 129	Near or above optimal
130 - 159	Borderline high
160 - 189	High
≥190	Very high
HDL cholesterol	
<40	Low
≥60	High
Triglyceride	
<150	Near
150 - 199	Borderline high
200 - 499	High
≥500	Very high

The chylomicrons are cleared from the circulation by the action of lipoprotein lipase, which is located on the surface of the endothelium of the Capillaries. The

enzyme catalyzes the breakdown of the triglyceride in the chylomicrons to FFA and glycerol, which then enter adipose cells and are reesterified. Alternatively, the FFA remain in the circulation bound to albumin. Lipoprotein lipase, which requires heparin as a cofactor, also removes triglycerides from circulating very low density lipoproteins (VLDL)[33] .

Chylomicrons and VLDL contain APO C, a complex of proteins that separates from them in the capillaries. One component of the complex, apolipoprotein C-II,activateslipoproteinlipase.

Chylomicrons depleted of their triglyceride remain in the circulation as cholesterol-rich lipoproteins called chylomicron remnants, which are 30-80 nm in diameter. The remnants are carried to the liver, where they bind to chylomicron remnant and LDL receptors. They are immediately internalized by receptor-mediated endocytosis, and are degraded in lysosomes.

The chylomicrons and their remnants constitute a transport system for ingested exogenous lipids . There is also an endogenous system made up of VLDL, intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), which transports triglycerides and cholesterol throughout the body[35].

VLDL are formed in the liver and transport triglycerides formed from fatty acids and carbohydrates in the liver to extrahepatic tissues. After their triglyceride is largely removed by the action of lipoprotein lipase, they become IDL. The IDL give up phospholipids and, through the action of the plasma enzyme lecithin-cholesterol acyltransferase (LCAT), pick up cholesteryl esters formed from cholesterol in the HDL. Some IDL are taken up by the liver. The remaining IDL then lose more triglyceride and protein, in the sinusoids of the liver, and become LDL. During this conversion, they lose APO E, but APO B-100remains.

LDL provide cholesterol to the tissues. The cholesterol is an essential constituent in cell membranes and is used by gland cells to make steroid hormones. In the liver and most extrahepatic tissues, LDL are taken up by receptor-mediated endocytosis in coated pit.. The receptors recognize the APO B-100 component of the LDL . They also bind APO E but do not bind APO-B48[33].

The human LDL receptor is one member of a family of receptors specialized for transport of macromolecules into cells via endocytosis in clarthrin-coated pits.

LDL are also taken up by a lower-affinity system in the macrophages and some other cells. In addition, macrophages preferentially take up LDL that have

been modified by oxidation. Oxidation can also occur in macrophages. Large doses of antioxidants such as vitamin E appear to slow the progress of atherosclerosis in experimental animals, but to date, results in humans have been disappointing. The LDL receptor on macrophages and related cells is called the scavenger receptor. It is different from the receptor on other cells and has a greater affinity for altered LDL. When the macrophages become overloaded with oxidized LDL, they become the "foam cells" that are seen in earlyatherosclerotiClesions[33].

In the steady state, cholesterol leaves as well as enters cells. Cholesterol appears to leave cells via one of the ABC cassette proteins , and this cholesterol is taken up by HDL. These lipoproteins are synthesized in the liver and the intestine.

A separate HDL receptor has now been identified and cloned. It is found primarily in endocrine glands that make steroid hormones and in the liver. The HDL system transfers cholesterol to the liver, which is then excreted in the bile. In this way it lowers plasma cholesterol.

APO E is synthesized by cells in the brain, spleen, lung, adrenal, ovary, and kidney, as well as the liver. Its concentration is greatly increased in injured nerves, where it appears to play a role in nerve regeneration. The apolipoprotein

E gene is present in the general population in three alleles: APO-2, APO-3, and APO-4. APO-4 is less common than APO-2 and APO-3 but is overrepresented in patients with Alz-heimer's disease and seems to predispose to this disease[33].

HYPERLIPOPROTEINEMIA

A number of diseases cause elevations in the concentrations of one or more lipoprotein classes in the plasma. In general these abnormalities are detected by the finding of an elevated concentration of triglyceride or cholesterol in the fasting plasma, a condition called hyperlipidemia[23].

CLINICAL FEATURES OF HYPERLIPIDEMIA[23]

1. Coronary heart disese
2. Peripheral vascular disese
3. Lipid deposition in soft tissues
    - Tendon xanthoma
    - Palmar xanthoma
    - Xanthelasma
    - Eruptive xanthoma
    - Corneal arcus

4. Lipemia retinalis

5. Acute pancreatitis

CLASSIFICATION:

Hyperlipedemia can be classified into

1. Primary – due to hereditary defects in lipoprotein metabolism

2. Secondary – manifestation of some other conditions

Table:4 Primary hyperlipidemia

Genetic disorder	Biochemical defects	Lipoprotein elevation
Familial lipoprotein lipase deficiency	Deficiency of lipoprotein lipase	Chylomicrons
Familial apoprotein – CII deficiency	Deficiency of apoprotein – CII	Chylomicrons, VLDL
Familial type III hyper lipoprotenemia	Abnormal apo – E of VLDL	Chylomicrons remnants & ILDL
Familial Hypercholesterolemia	Deficiency of LDL receptor	LDL

Familial Hyper triglyeridemia	Unknown	VLDL

Secondary Hyperlipedemia

Common causes are[23]

1. Diabetes
2. Hypothyroidism
3. Alcohol consumption
4. Collagen disorder
5. CRF
6. Nephrotic syndrome

LABORARTORY EVIDENCE:

As a working rule, hyperlipoprotenemia is considered to be present

1. When the plasma cholesterol exceeds 200mg/dl
2. When the triglycerides level exceeds 200mg/dl

HYPO LIPOPROTENEMIA

Hypolipoprotenemis is considered when the total cholesterol concentration is less than 100mg/dl

Hypo lipoprotenemia is either due to

1. Hereditary triad (rare)

2. Secondary to number of diseases

Hypo beta lipoprotenemia[23]

Due to mutations in the gene for apo B 100. That disturbs the synthesis or produces truncated form of apo – B 100.

Characterized by very low cholesterol and triglyceride level.

CLINICAL FEATURES:

Malabsorption of fat

Ataxia

Neuropathy

Retinitis pigmentosa

Acantho cytosis

Treated with vitamin E

SECONDARY HYPO LIPOPROTENEMIA[23]

Common causes are

1. Malnutrition associated with – low total cholesterol
2. Alcoholism & GI tract diseases- low LDL
3. Hyper thyroidism – low total cholesterol
4. Uncontrolled AIDS – low total cholesterol
5. Acute & chronic myeloid leukemia – low LDL
6. Gauchers and Niemann pick's disease – low LDL & HDL.

LIPID ABNORMALITIES IN ACTIVE RHEUMATOID ARTHRITIS

Patient with active rheumatoid arthritis exhibit various lipid abnormalities, when compared with controls, the common abnormalities are[17,20,38,41,54],

1. Decreased serum lipid level
2. Decreased total cholesterol level
3. Decreased LDL cholesterol level
4. Decreased HDL cholesterol level
5. Decreased Triglyceride level

6. Elevated lipoprotein (a) level

EXPLANATION FOR DYSLIPOPROTENEMIA IN RHEMATOID ARTHRITIS

1. The reduction of Total cholesterol in active RA is due to reduced synthesis and increased clearance through scavenger receptor pathway[38]

2. Oxidative modification of LDL is also important and is of special interest, that the product of LDL oxidation may be recognized by the scavenger receptor, leading to the increased uptake of modified lipoprotein particles by macrophages. They may be directly cytotoxic to endothelial cells, chemotactic for inflammatory cells and causes functional changes in smooth muscles. The inflammatory environment and disturbed anti oxidant mechanism in RA may promote LDL cholesterol oxidation, thereby facilitating atherogenesis at low lipoprotein concentration. Use of anti oxidants may lower the cardiovascular mortality.[44]

3. The presence of circulating anti oxidized LDL antibodies in RA, may be responsible for the reduced level of total cholesterol and LDL cholesterol.[48]

4. Increased Cholesterol ester transfer protein (CETP) activity is associated with low HDL-C levels in RA patients.[36]

5. The reduced HDL-C level in RA patient compared to controls may be due to physical inactivity in RA patients.[37]

VARIOUS STUDIES ON LIPID PROFILE IN RHEUMATOID ARTHRITIS PATIENTS.

1.**Lipid profile in Rheumatoid arthritis and its relation to disease activities[43]**

By vottery R, saigal R, singhal N, Gupta Bs.

Department of medicine, SMS hospital, Jaipur

Lipid profiles of 25 rheumatoid arthritis cases were compared with age and sex matched controls. Serum triglyceride & total cholesterol were found to be significantly lowered in RA patients, while serum LDL & HDL cholesterol were not altered significantly.[43]

-JAPI 2001 Dec: 49:1188 - 90

2.**Dyslipoprotenemia in the course of active rheumatoid arthritis**[20]

-By Lazarevic MB, vatic J, M iadenovic V, Myones bl, skosey JL, swedler WL.

Department of medicine, University of Illinois, Chicago

Concentration of serum lipids and serum LDL were measured, and agarose gel electrophoresis of serum lipoprotein were performed in 69 persons of RA and 65 healthy blood donors. RA patients had significantly decreased concentration of total serum lipids & serum cholesterol, LDL & HDL. Compared with healthy blood donors, RA patients with severe disease activity has significantly reduced cholesterol in LDL & HDL, compared with patients with minimal disease activity.[20]

- Semin arthritis Rheum 1992 Dec; 22(3); 172-8

3.**Hypocholesterolemia & abnormal high density lipoprotein in rheumatoid arthritis**[18]

-By Lorber M, Aviram M, Linn S, Scharf Y, Brook JG.

Plasma lipids & lipoprotein patterns were determined in 54 female RA patients.

There was 26% reduction in total cholesterol, 36% reduction in both LDL & HDL were observed. Plasma apo A – 1, the major HDL protein was in the

normal range suggesting an abnormal HDL fraction, even though reduced HDL was found in RA patient, HDL/LDL ratio was normal and apo A 1/ apo – B ratio was increased, suggesting that these patients are at increased risk of atherosclerosis.[18]

- Br j Rheumatol 1985 Aug: 24(3);250-5

4.**Serum total, HDL, LDL, cholesterol and triglycerides levels in patients with rheumatoid arthritis[40].**

-By Lakatos J, Harsagyi A, United sanitary institution, pecs, Hungary.

In this study, patients with rheumatoid arthritis (26 men, 103 women) the serum total cholesterol, HDL cholesterol & triglycerides were lowered when compared to controls. (625 men & 749 women).[40]

5.**Serum lipoprotein in active Rheumatoid arthritis and other chronic inflammatory arthritis. Relativity to inflammatory activity[38].**

-By svenson KL,Lithell H, Hallgren R, Selinus I,Vessby B.

Department of internal medicine, University hospital, Uppasala, Sweeden

Lipid metabolism was found in 69 patients with untreated rheumatoid arthritis (48) and in sero negative spondylo arthropathies. (21). The patients had high inflammatory activity as measured by ESR & CRP. Serum cholesterol and cholesterol levels in VLDL, LDL & HDL were reduced by 20% to 30%. The

triglyceride level in VLDL & HDL were reduced by 10% to 30% compared to healthy controls.[38]

There was significant correlation between the inflammatory activity and certain lipoprotein level

-Arch Intern Med .1987 Nov;147(11); 1912-6

6.**lipoprotein (a), lipids and lipoproteins in patients with rheumatoid arthritis**[41]

-By Rantapaa – Dahlgvist S, Wallberg – Jonsson S, Dahlen G.

Department of rheumatology, university hospital, Umea, Sweeden

Lipoprotein (a), an independent atherogenic factor was significantly increased in 93 patients with sero positive RA. The plasma concentration of cholesterol & HDL in both male & female patients were lower than in controls.[41]

-Ann Rheum Dis 1991 Jun, 50(6) ; 366-8

7.**Dyslipidemia & rheumatoid arthritis**[37]

-By Munro R, Morrison E, Mc Donald AG.

The inflammatory environment and disturbed anti oxidant mechanism in rheumatoid arthritis may promote LDL oxidation, thereby facilitating atherogenesis.[37]

8.**serum oxidized low density lipoprotein in RA[58]**

-By Kim SH, Lee CK, Lee EY, park SY, Choys, Yoo B.

Division of allergy & rheumatology, Department of medicine, University of Ulsan college of medicine, Orsan medical centre, Seoul, Korea.

Compared with healthy women, those with active RA, had increased serum oxidized LDL level, which may contribute to the increased risk of cardiovascular diseases in these group of patients.[58]

-Rheumatol Int. 2003 Nov 20

9.**Increased level of anti oxidant LDL antibodies are associated with reduced level of cholesterol in general population[59].**

-By Tinahones FJ, Gomez – Zumaquero JM, Cardona F.

Carlos Haya, regional hospital, Malaga, Spain.

This study shows the relationship between the level of auto antibodies to oxidized LDL & lipoprotein in a population of 400 patients. Anti oxidized LDL

antibodies were measured by ELISA and total cholesterol, triglyceride, HDL were measured by commercial kits. Subjects who were positive for anti oxidized LDL antibodies had significantly lowered level of total cholesterol & LDL cholesterol.[59]

-Metabolism. 2002 Apr, 51(4); 429-31

10.**Effect of anti rheumatic therapy on serum lipid levels in patients with RA[39].**

-By Park YB, Choi HK, Kim MY, Lee WK , Song J.

Division of rhuematology, Dept. Of medicine, Yonsei university college of medicine, Seoul, Korea.

Active rheumatoid arthritis is associated with adverse lipid profile that improves following effective treatment of RA. This improvement may reduce the risk of cardiovascular disease.[39]

MATERIALS & METHODS

SETTINGS: Patients attending Rheumatology outpatient department, Madras Medical College and Government general hospital Chennai - 600 003.

ETHICAL APPROVAL:

Obtained

STUDY DESIGN:

To Study the lipid profile abnormalities in rheumatoid arthritis patients , and the correlation between lipid abnormalities and severity of the disease

a cross sectional study design was chosen.

PERIOD OF STUDY:

January 2008 to September 2008

SAMPLE SIZE

Cases: 50, Controls: 50 .

INCLUSION CRITERIA:

1. Arthritis of hand joints:
2. Soft tissue swelling of 3 or more than 3 joints
3. Morning stiffness for atleast one hour.
4. Symmetrical arthritis
5. Positive rheumatoid factor

EXCLUSION CRITERIA:

1. Patients with rheumatoid arthritis with the following conditions were excluded from the study

1. Malabsorption syndrome
2. Nephrotic syndrome
3. Diabetes mellitus
4. Thyroid disorders
5. Liver disorders
6. Intake drugs like
    a. Diuretics
    b. Oral contraceptives
7. Lipid storage disorders

STUDY POPULATION:

Fifty patients of Rheumatoid arthritis and fifty age and sex matched healthy controls were selected for the study from Rheumatology clinic and outpatient department of Institute of Internal Medicine, Government General hospital Chennai, after thorough history taking and clinical examination and by exclusion criteria..

All the RA patients were selected on the basis of 1987 revised criteria of American rheumatism Association for the classification of rheumatoid arthritis.

Fifty patients with the age group ranging from 20 to 70 years were studied, they were at different stages of rheumatoid arthritis.

Age & sex matched healthy persons, between the age of 20 to 70 years were taken for the control study.

LABAROTARY MEASUREMENTS

In all the cases latex fixation test for rheumatoid factor was done.

After ensuring 12 hours overnight fasting, normal diet (without any fat restriction) for previous two weeks, and abstinence from alcohol, the blood samples were collected from RA patients & healthy controls. From the blood, serum was separated & stored in refrigerator. Then this was used for lipoprotein analytical studies.

Concentration of total cholesterol, HDL-cholesterol, and triglycerides were assessed enzymatically with commercially available reagents. Concentration of LDL- cholesterol was calculated by use of the Friedewald equation for participants who had triglycerides (< 400 mg/dl)

$$LDL = TC - HDL\text{-}c - TGL/5.$$

The marker of inflammation like ESR was measured by Wintrobe's method.

FINANCIAL SUPPORT: nil.

CONFLICT OF INTEREST: nil.

STATISTICAL ANALYSIS

Statistical analysis was carried out for 100 participants [50 RA patients, 50 controls] after categorizing each variable. Base line data was collected from patients Age, sex, duration of early morning stiffness,Lipid profile, ESR were analyzed.

The significance of difference in mean between two groups were analyzed by student t-test. The correlation between Lipid profile and

ESR, early morning stiffness calculated by using the Pearson's correlation coefficient method.

Statistical significance was taken when p value < 0.05. Statistical analysis was carried out using standard formulae. Microsoft excel 2007 and SPSS (statistical package for social sciences) version 13 software was used for data entry and analysis.

RESULTS AND OBSERVATION

In our study , 50 RA patients matched with 50 healthy controls were studied for lipid abnormalities and the following observation were made. Patients with age group ranging from 20 to 70 years were studied.

Table:5 AGE DISTRIBUTION IN THIS STUDY

AGE IN YEARS	NUMBER OF PATIENTS	PERCENTAGE %
20 - 30	15	30%
31 - 40	14	28%
41 - 50	9	18%

51 - 60	9	18%
61 - 70	3	6%

In this study, Rheumatoid arthritis diseased patients lies more in the age group of 20 to 40 years.

Table:6 SEX DISTRIBUTION IN THIS STUDY

SEX	NUMBER OF PATIENTS	PERCENTAGE
FEMALE	43	86%
MALE	7	14%

This study shows females are affected more than males.

Table:7 LIPID PROFILE IN STUDY GROUP –STATISTICAL ANALYSIS

	TC(mgs/dl)	LDL(mgs/dl)	TGL(mgs/dl)	HDL(mgs/DL)	TC/HDL Ratio
MEAN	158.64	96	148.68	32.32	4.96
MEAN DEVIATION	8.12	7.84	14.88	3.28	0.49

STANDARD DEVIATION	9.59	9.15	17.7	3.96	0.59
STANDARD ERROR OF MEAN	1.36	1.29	2.50	0.56	0.08
STANDARD ERROR OF DIFFERENCE BETWEEN THE TWO MEAN	2.78	2.88	3.06	0.93	0.16

Table:8 LIPID PROFILE IN CONTROL GROUP –STATISTICAL ANALYSIS

	TC(mgs/dl	LDL(mgs/dl	TGL(mgs/dl	HDL(mgs/DL)	TC/HDL Ratio
MEAN	172.6	106.5	166.32	32.46	5.45
MEAN DEVIATION	13.59	9.33	9.30	4.19	0.79
STANDARD DEVIATION	17.18	18.20	12.43	5.24	0.97

STANDARD ERROR OF MEAN	2.43	2.57	1.76	0.74	0.14

Table: 9 COMPARISION OF STUDY AND CONTROL GROUP MEAN

	TC(mgs/dl)	LDL(mgs/dl)	TGL(mgs/dl)	HDL(mgs/DL)	TC/HDL Ratio
STANDARD ERROR OF DIFFERENCE BETWEEN THE TWO MEAN	2.78	2.88	3.06	0.93	0.16
t-TEST VALUE	-5.017	-3.645	-5.767	-0.151	-3.052
P" VALUE	<0.0001	0.0004	<0.0001	0.8806	0.0029

In this study TC, LDL-C, TGL ,TC/HDL are significantly reduced and HDL-C not significantly reduced.

Table:10 COMPARISION OF LIPID VALUES IN STUDY AND CONTROL GROUPS

GROUP	TC(mgs%)	LDL	TGL	HDL	TC/HDL
STUDY	158±9.59	96±9.15	148.7±17.7	32.3±3.96	4.96±0.59
CONTROL	172.6±17.2	106.5±18.2	166.3±12.4	32.5±5.24	5.45±0.97

This study shows reduced TC, LDL-C, TGL, TC/HDL , when compared to controls.

Table:11 COMPARATIVE ANALYSIS OF LIPID DISORDER

TYPE OF LIPID DISORDER	NO. OF PATIENT		PERCENTAGE	
	STUDY	CONTROL	STUDY	CONTROL
TC>200	0	2	0%	4%
LDL>130	0	4	0%	8%
TGL>150	21	44	42%	88%
HDL<40	48	44	56%	88%
>40	2	6	4%	12%
TC/HDL >6	3	17	6%	34%

Table: 12 E.S.R. LEVEL – AN ANALYSIS IN THIS STUDY

ESR LEVEL(mm/hr)	NO. OF PATIENTS	PERCENTAGE %
<40	4	8%
41 - 60	10	20%
61 - 80	15	30%
>80	21	42%

Increased ESR >80 mm/hr found in 42% of RA patients.

Figure: 13 COMPARISION OF ESR BETWEEN STUDY AND CONTROL GROUP

GROUP	**MEAN±SD OF ESR**	**STANDARD ERROR OF DIFFERENCE BETWEEN TWO MEAN**	**t-TEST**	**P VALUE**
STUDY	**74.52±19.9**			
CONTROL	**11.96±4.7**	**2.89**	**21.64**	**<0.0001**

ESR is significantly raised in RA patients when compared to controls.

Table:14 MORNING STIFFNESS DISTRIBUTION IN STUDY GROUP

MORNING STIFFNESS(min)	NO. OF PATIENTS	PERCENTAGE %
<30 min	5	10%
31 – 60 min	30	60%
>60 min	15	30%

Table:15 CORRELATION BETWEEN AGE AND TOTAL CHOLESTEROL LEVEL

AGE(YEARS)	<100 mgs%		101 – 150 mgs%		151 – 200 mgs%		>200 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
20 - 40	0	0	4	8	26	21	2	0
41 - 60	0	0	2	2	13	16	0	0
>60	0	0	0	0	3	3	0	0

In the study group, TC levels in 40 patients were in the range of 151- 200 mgs% , out of which 21 patients lie in the age group of 20 to 40 years.

Table:16 CORRELATION BETWEEN SEX AND TOTAL CHOLESTEROL LEVEL

SEX	<100 mgs%		101 – 150 mgs%		151 – 200 mgs%		>200 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
FEMALE	-	-	6	9	35	34	2	-
MALE	-	-	1	1	6	6	-	-

Table:17 CORRELATION BETWEEN AGE AND LDL CHOLESTEROL LEVEL

AGE(YEARS)	<60 mgs%		61 – 80 mgs%		81 – 100 mgs%		>100 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
20 - 40	0	0	4	4	4	20	24	5
41 - 60	0	0	0	1	6	10	9	7
>60	0	0	0	0	1	2	2	1

In the study group, LDL-C level in 13 patients was >100 mgs% , out of which 7 patients lies in the age group of 41 to 60 years.

Table: 18 CORRELATION BETWEEN SEX AND LDL CHOLESTEROL LEVEL

SEX	<60 mgs%		61 – 80 mgs%		81 – 100 mgs%		>100 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
FEMALE	-	-	4	5	10	28	29	10
MALE	-	-	-	-	1	4	6	3

Table:19 CORRELATION BETWEEN AGE AND TRIGLYCERIDE LEVEL

AGE(YEARS)	<100 mgs%		101 – 140 mgs%		141 – 180 mgs%		>180 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
20 - 40	0	0	2	9	27	20	3	0
41 - 60	0	0	0	7	14	11	1	0
>60	0	0	0	0	2	3	1	0

In the study group, TGL level in 34 patients were in the range of 141- 180 mgs% , out of which 20 patients lies in the age group of 20 to 40 years.

Table:20 CORRELATION BETWEEN SEX AND TRIGLYCERIDE LEVEL

SEX	<100 mgs%		101 – 140 mgs%		141 – 180 mgs%		>180 mgs%	
	controls	cases	controls	cases	controls	cases	controls	cases
FEMALE	-	-	2	15	38	28	3	-
MALE	-	-	-	1	5	6	2	-

Table:21 CORRELATION BETWEEN AGE AND HDL CHOLESTEROL LEVEL TC/HDL RATIO

AGE(YEARS	HDL<30 mgs%		HDL 31 - 35 mgs%		HDL 36 – 40 mgs%		HDL >40 mgs%		TC /HDL >6	
	controls	cases	controls	cases	controls	cases	controls	cases	controls	cases
20 - 40	12	10	7	10	9	9	4	0	10	3
41 - 60	8	6	5	8	2	3	0	1	6	0
>60	1	3	2	0	0	0	0	0	1	0

In the study group, only one patient had HDL-C >40 mgs%.and 3 patients had TC/HDL>6.

Table:22 CORRELATION BETWEEN SEX AND HDL CHOLESTEROL LEVEL TC/HDL RATIO

SEX	HDL<30 mgs%		HDL 31 - 35 mgs%		HDL 36 – 40 mgs%		HDL >40 mgs%		TC /HDL >6	
	controls	cases	controls	cases	controls	cases	controls	cases	controls	cases
FEMALE	20	15	9	16	10	11	4	1	16	3
MALE	1	4	5	2	1	1	-	-	1	-

Table:23 CORRELATION BETWEEN LIPID ABNORMALITY AND ESR

ESR(mm/hr)	TOTAL NO. OF PATIENT	TC(mgs%)	LDL(mgs%)	TGL(mgs%)	HDL(mgs%)	TC/HDL
20 - 40	4	171±3.82	105± 3.7	158 ±16.8	34± 1.4	5± 0.21
41 - 60	10	168.3±5.9	102 ±5.2	156.5± 12.4	34.3± 2.2	4.9± 0.37
61 - 80	15	156.4±8.6	92.5± 9.7	155± 15.8	32.5± 5.2	4.9± 0.74
>80	21	153.3±7	93.8± 8.6	138.7± 17.9	30.9± 3.6	5 ±0.62

This study shows negative correlation between ESR and lipids .

Table:24 CORRELATION BETWEEN LIPID ABNORMALITY AND EARLY MORNING STIFFNESS

EARLY MORNING STIFFNESS	TOTAL NO. OF PATIENT	TC(mgs%)	LDL(mgs%)	TGL(mgs%)	HDL(mgs%)	TC/HDL
≤30 min	5	164.4 ±14.6	100± 10.9	166.4± 10	33.2± 5.2	5.1± 0.91
31 – 60 min	30	152.3± 17.3	95.7± 8.5	158.5± 9.1	32.8± 4	4.9 ±0.54
>60 min	15	136.3± 13.1	96.8± 9.9	156.3± 9.9	31.1 ±3.6	5.1± 0.59

This study, shows that TC and TGL cholesterols negatively correlate significantly with duration of early morning stiffness in RA patients.Whereas LDL-C, HDL-C are negatively correlating insignificantly with duration of early morning stiffness.

DISCUSSION

The complete analysis of 50 Rheumatoid arthritis patients were done. The 50 age & sex matched health persons were taken as controls.

They were studied on the basis of clinical features, biochemical features, radiological features with special reference to lipid profile. Some characteristic features noted in the study are given below.

In this study out of 50 cases, 43 were females, 7 were males. The female to male ratio was 6.14:1.

The age of the patient ranged from 20 to 70 years with mean age 40.38±12.64 in study group and 40.04±11.7 in control group.

All the 50 patients (100%) fulfilled the revised criteria of American Rheumatism Association for Rheumatoid arthritis[25].

LIPID PROFILE ABNORMALITIES IN RHEUMATOID ARTHRITIS:

PATIENTS & CONTROLS

TOTAL CHOLESTEROL:

Total cholesterol was significantly reduced in rheumatoid arthritis patients, when compared to controls. The total cholesterol levels in our patients was 158.64± 9.59. In controls, the level was 172.6± 17.18.(p value of <0.0001)

LDL cholesterol:

LDL cholesterol was significantly reduced in RA patients, when compared to controls. In our patients, LDL-C level was 96± 9.14. In control, the level was 106.5 ± 18.20 (p value < 0.0004)

TRIGLYCERIDES:

Triglyceride level was also significantly reduced in RA patients, when compared to controls. In our patients, the triglyceride level was 148.68± 17.7. In controls, it was 166.32± 12.43. (p value < 0.0001)

HDL CHOLESTEROL

In our study, HDL-C cholesterol was not significantly reduced, when compared to controls. In our study, it was 32.32± 3.96. In controls, it was 32.46± 5.24.(p value is 0.8806)

TC/HDL LEVEL:

In our study, TC/HDL level was significantly reduced when compared to controls. In our patients, it was 4.96± 0.59. In controls, it was 5.45± 0.97 (p = 0.0029)

Thus from this study, serum total cholesterol, LDL cholesterol & triglyceride were significantly lower in RA patients, as compared to controls, while serum HDL cholesterol was not significantly altered in RA patients. TC/HDL ratio was also significantly reduced.

CORRELATION WITH AGE:

In our study, out of 50 Rheumatoid arthritis patients, 29 patients were in the age group of 20 to 40 years.

- Total cholesterol in eight patients were in the range of 101 to 150 mg% and in 21 patients were in the range 151 to 200 mg% .
- LDL –C in four patients were in the range of 61 to 80mg% , 20 patients were in the range of 81 to 100mg% and in 5 patients were above 100mg%
- TGL in nine patients were in the range 101 to 140mg% and 20 patients were in the range of 140 to 180mg% . No patients had above 180 mg% of TGL.
- HDL-C in ten patients were below 30mg% , 10 patients were in the range of 31 to 35mg% and in 9 patients were in the range of 36 to 40 mg%. No patient had above 40mg%.
- The TC/HDL ratio in three patients were above 6.

OUT OF 18 PATIENTS IN THE AGE GROUP OF 41 TO 60 YEARS

- TC in two patients were in the range of 101 to 150 mg% ,and in 16 patients were in the range of 151 to 200 mg% .
- LDL-C in one patient was in the range of 61 to 80mg% , 10 patients were in the range of 81 to 100mg% and in 7 patients were above 100 mg% .
- TGL in seven patients were in the range of 101 to 140 mg% .and in 11 patients were in the range of 141 to 180 mg% .
- HDL-C in six patients were below 30mg% , 8 patients were between 31 to 35 mg% and 3 patients were in the range of 36 to 40 mg% . One patient had above 40mg%.
- No patient was above 6 in TC/HDL ratio.

Out of three patients, above 60 years.

- TC in 3 patients were in the range of 151 to 200 mg%. LDL-C in 2 patients were in the range of 81 to 100 mg% and in one patient was more than 100mg% .
- TGL in three patients were in the range of 141 to 180mg% .
- HDL-C in three patients were below 30mg% .
- TC/HDL ratio above 6 was not found in this age group.

CORRELATION WITH SEX:

- In this study of 50 RA patients 43 were female patients & 7 were male patients.

- TC in nine female patients were in the range of 101 to 150mg%, one male patient was in the range of 101 to 150mg% ,34 female patients and in six male patients were in the range of 151 to 200 mg% .
- LDL-C in five female patients were in the range of 61 to 80mg%. 29 female patients & 4 male were in the range of 81 to 100mg% . 10 female patients and in 3 male were above 100mg% .
- TGL in fifteen female patients and in one male patient were in the range of 101 to 140mg%. 28 female and in 6 male patients were in the range of 141 to 180mg% .
- HDL-C in fifteen female and in 4 male patients were below 30mg%. 16 female and in 2 male patients were in the range of 31 to 35 mg% . 11 Females and in 1 male patient were in the range of 36 to 40mg% . HDL-C in one female patient was more than 40mg%.
- TC/HDL ratio in three female patients were more than 6.

CORRELATION WITH ESR:

- In this study, 4 patients had ESR less than 40mm/hr, with TC 171± 3.82, LDL-C 105± 3.7, TGL 158 ± 16.8, HDL-C 34 ± 1.4 and TC/HDL was 5± 0.21.

- The ESR in ten patients was between 41 to 60 mm/hr, with TC 168.3± 5.9, LDL-C 102 ±5.2, TGL 156.5± 12.4, HDL-C 34.3± 2.2 and TC/HDL ratio was 4.9± 0.37.
- The ESR in fifteen patients was between 61 to 80 mm/hr, with TC 156.4± 8.6, LDL-C 92.5± 9.7, TGL 155 ±15.8, HDL-C 32.5± 5.2 and TC/HDL was 4.9± 0.74.
- The ESR in twenty one patients was more than 80 mm/hr, with TC 153.3 ±7, LDL-C 93.8± 8.6, TGL 138.7 ±17.9, HDL-C 30.9± 3.6 and TC/HDL was 5± 0.62.

In our study Pearson correlation between ESR and lipids shows

- Inverse correlation of ESR with TC ($r=-0.701$,$p<0.0001$)
- Inverse correlation of ESR with LDL-c ($r= -0.436$, $p=0.0015$)
- Inverse correlation of ESR with TGL ($r= -0.454$,$p= 0.0009$)
- Inverse correlation of ESR with HDL ($r= -0.388$,$p= 0.0054$ **)**

- From this study, it can be concluded that, in RA patients lipid profile abnormalities is negatively correlated significantly with ESR.

CORRELATION WITH EARLY MORNING STIFFNESS:

- In this study, 5 patients had early morning stiffness of less than 30 min., with total cholesterol was 164.4 ± 14.6, LDL-C was 100± 10.9, TGL was 166.4 ±10, HDL-C was 33.2± 5.2 & TC/HDL ratio was 5.1± 0.91.

- Thirty patients had early morning stiffness of between 31 to 60 min., with total cholesterol was 152.3 ±17.3, LDL-C was 95.7± 8.5, TGL was 158.5± 9.1, HDL-C was 32.8± 4 & TC/HDL ratio was 4.9± 0.54.
- Early morning stiffness of more than 60 min in fifteen patients., with total cholesterol was 136.3 ±13.1, LDL-C was 96.8± 9.9, TGL was 156.3± 9.1, HDL-C was 31.1± 3.6 & TC/HDL ratio was 5.1± 0.59

In our study Pearson correlation between Early morning stiffness and lipids shows

- Inverse correlation of TC with Morning stiffness (**r= -0.337, p= 0.0166**)
- Inverse correlation of LDL with Morning stiffness (**r= -0.103 , p= 0.4746**)
- Inverse correlation of TGL with Morning stiffness (**r= -0.509 , p=0.0002**)
- Inverse correlation of HDL with Morning stiffness (**r= -0.211 , p=0.1419**)

From this study, it can be concluded that TC and TGL cholesterols negatively correlate significantly with duration of early morning stiffness

in RA patients.Whereas LDL-C, HDL-C are negatively correlating insignificantly with duration of early morning stiffness.

COMPARISION OF PREVIOUS STUDIES WITH PRESENT STUDY

Table:25 COMPARISION OF GEORGIADIS et al[36] WITH PRESENT STUDY

LIPID	PRESENT STUDY			GEORGIADIS et al		
	STUDY	CONTROL	P Value	STUDY	CONTROL	P value
TC(mean±SD)	158.64 ± 9.59	172.6±17.18	0.0001	216±50.3	296.4	<0.001
TGL(mean±SD)	148.68±17.7	166.32±12.43	0.0001	133± 58.2	69.6	<0.001
HDL(mean±SD)	32.32±3.96	32.46±5.24	0.8803	47.5± 11.8	63.6	<0.001
LDL(mean±SD)	96±9.15	106.5±18.20	0.0004	141±42.3	126.5±31.3	<0.001
TC/HDL	4.96 ±0.59	5.45±0.97	0.0029	4.9±1.3	3.7±0.9	<0.001

IN **GEORGIADIS et al[36]** study significantly raised TC,LDL, TGL, , TC/HDL with reduced HDL. TC and HDL are negatively correlated significantly with CRP and ESR. Increased CETP activity is found in RA patients with low HDL-C levels.

In our study, TC,LDL, TGL ,TC/HDL are significantly reduced with insignificant reduction in HDL levels in RA compare to controls. A significant negative correlation is present between all lipid parameters and ESR.

Table:26 COMPARISION OF VEIL COBANKARA et al [57]WITH PRESENT STUDY

LIPID	PRESENT STUDY			VEIL COBANKARA et al		
	STUDY	CONTROL	P Value	STUDY	CONTROL	P Value
TC (mean±SD)	158.64 ± 9.59	172.6±17.18	0.0001	188.4±41.8	185±19.3	NS
LDL (mean±SD)	96±9.15	106.5±18.20	0.0004	123.4±24.6	113.3±21.1	NS
TGL (mean±SD)	148.68±17.7	166.32±12.43	0.0001	124.5±50.1	94.6±24.9	<0.001
HDL (mean±SD)	32.32±3.96	32.46±5.24	0.8803	40±7.4	52.8±4.8	<0.001
TC/HDL	4.96 ±0.59	5.45±0.97	0.0029	4.7±1.5	3.5±0.7	<0.01

In **VEIL COBANKARA et al[57]** study, significantly reduced HDL, increased TGL were found. TC, and LDL were insignificantly raised when compared to controls.Lipoprotein(a) significantly raised.

Table:27 COMPARISION OF ASANUMA et al[56] WITH PRESENT STUDY

LIPID	PRESENT STUDY			ASANUMA et al[56]		
	STUDY	CONTROL	P Value	STUDY	CONTROL	P Value
TC (mean±SD)	158.64 ± 9.59	172.6±17.18	0.0001	192± 42	185±42	>0.05
LDL (mean±SD)	96±9.15	106.5±18.20	0.0004	119 ±33	117±31	>0.05
TGL (mean±SD)	148.68±17.7	166.32±12.43	0.0001	112±69	125±83	>0.05
HDL (mean±SD)	32.32±3.96	32.46±5.24	0.8803	50±16	50±13	>0.05

In this study, TC, LDL, TGL and HDL were all had insignificant difference when compared to controls.

Table:28 COMPARISION OF RANTAPAA-DAHLAVIST[41] et al WITH PRESENT STUDY

LIPID	PRESENT STUDY			RANTAPAA-DAHLAVIST et al[41]		
TC(mean)	STUDY	CONTROL	P Value	STUDY	CONTROL	P value
TGL(mean)	158.64	172.6	0.0001	219.6	296.4	0.001
HDL(mean)	148.68	166.32	0.0001	56.8	69.6	>0.05
	32.32	32.46	0.8803	56	63.6	<0.05

In **RANTAPAA-DAHLAVIST[41] et al** ,TC and HDL were significantly reduced whereas TGL was insignificantly reduced when compared to controls.

Table:29 COMPARISION OF PREVIOUS STUDIES WITH PRESENT STUDY

STUDY	TC	LDL	TGL	HDL	LP(a)	TC/HDL
Lazarevic et al[20]	↓(S)	↓(S)	↓(S)	↓(S)	-	-
Rantapää-Dahlqvist et al[41]	↓(S)	-	↓(NS)	↓(S)	-	-
Svenson et al[38]	↓(S)	↓(S)	↓(S)	↓(S)	-	-
Kakati et al[54]	↓(S)	↓(S)	↓(S)	↓(S)	-	-
Park YB,et al[17]	↓(NS)	↓(NS)	↓(NS)	↓(S)	↑(S)	-
Georgiadis et al[36].	↑(S)	↑(S)	↑(S)	↓(S)	-	↑(S)
Veil cobankara et al[57]	↑(NS)	↑(NS)	↑(S)	↓(S)	↑(S)	↑(S)
Asanuma et al[56]	↑(NS)	↑(NS)	↓(NS)	No difference	↑(S)	-
Frati et al[19]	NS	NS	NS	NS	-	-

Magaro et al[53]	NS	NS	NS	↓(S)	-	-
Munro et al[37]	↓(S)	↓(S)	↓(S)	↓(S)	-	-
Vottery et al[43]	↓(S)	NS	↓(S)	NS	-	-
Lakatos et al[40]	↑(S)	↑(S)	↓(S)	↓(S)	-	-
Lorber et al[18]		↓(S)		↓(S)	-	-

↓ -Decreased

↑ -Increased

S –Significantly

NS –Not significantly

The lipid profile of patients with RA has been evaluated in several of the above studies . Most of the studies, Lazarevic et al, Rantapää-Dahlqvist et al, Svenson et al, Kakati et al, Park YB,et al, Munro et al, Nurmohamed Mt et al[15], had reported an overall reduction in all lipid sub-fractions in cases of active disease. Our study results are in line with above mention studies.

Georgiadis et al[36]. have reported significantly increased levels of TC, LDL, TGL, TC/HDL with reduced HDL-C.

Veil cobankara et al[57] had reported significantly increased TGL, TC/HDL with reduced HDL,whereas TC,LDL were insignificantly raised.

Asanuma et al[56], Frati et al[19], had reported insignificant difference between RA and controls. Magaro et al[53] reported except HDL other lipid subfractions are insignificantly changed.

Vottery et al[43] had reported significant reduced TC, TGL levels. Lakatos et al[40] had reported significantly raised TC, LDL, reduced TGL, HDL. Lorber et al[18] had reported significant reduced LDL, HDL.

Park YB,et al[17], Asanuma et al[56], Veil cobankara et al[57] had reported significantly raised Lipoprotein(a).

These contrasting results in various previous studies could be attributed to the size of the samples, the type of study (prospective or cross-sectional), differences in the disease type (established or early), or to differences in the disease activity.

The favourable lipid profile in our study cannot explain increased cardiovascular mortality in RA patients. The explanation given by western studies for increased cardiovascular mortality in RA patients as follows.

1. The inflammatory environment and disturbed antioxidant mechanisms in RA [44] may promote LDL oxidation, thereby facilitating atherogenesis at lower

ambient lipid concentrations and placing RA patients at higher cardiovascular risk. Though attractive, this hypothesis remains to be tested

2. presence of circulating autoantibodies to VLDL and LDL in active RA[48] . by forming immune complexes. may also have pre-atherogenic effects on the vascular wall .

3.cardiovascular disease in RA may result from accelerated atherosclerosis caused by clinical or subclinical vasculitis.[45]

4. Reduced cardiovascular fitness caused by immobility[37].

5. medication, increased homocysteine level[50], and increased thrombotic factors (fibrinogen, von Willebrand factor, plasminogen activator antigen, and fibrin D-dimer)[51]

6. . many similarities have emerged between the inflammation paradigm in the pathogenesis of atherosclerosis and the well established inflammation mechanism in the pathogenesis of RA[49 52]. These similarities raise the possibility that inflammatory mechanisms responsible for synovial lesions in patients with RA may directly participate in producing atherosclerotic lesions resulting in excess cardiovascular disease in RA patients[60].

7.Lipoprotein (a), an important independent factor in . atherogenesis and thrombogenesis[46] is increased in RA correlating positively with the acute phase response.[46 47].

Limitation in our study:

1. The limitation of this study is that there was no consideration and analysis of the effects of patients' average daily physical activity

2.The sample size was likely to be insufficient , thus we cannot rule out type II error in these results.

Further research examining the relation between cardiovascular mortality in RA dyslipidaemia, and the effects of chronic inflammation on vascular biology, lipids, and atherosclerosis might prove fruitful both to rheumatologists and cardiologists.

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CONCLUSION

The following conclusions were derived from our study.

1.Patients with Rheumatoid arthritis had significantly reduced levels of serum total cholesterol, LDL-cholesterol, triglyceride, as compared to controls.

2.HDL-cholesterol level was not significantly altered in Rheumatoid arthritis as compared to controls.

3.It is observed that there is significant negative correlation between the lipid parameters -TC, LDL-C, TGL, HDL-C in active Rheumatoid arthritis patients and erythrocyte sedimentation rate .

4. The lipid parameters TC, TGL were negatively correlated with duration of early morning stiffness ,whereas LDL-C, HDL are insignificantly correlating with duration of early morning stiffness in active Rheumatoid arthritis patients.

5. Though lipid profile is favourable in our study, there is increased cardiovascular mortality in Rheumatoid arthritis patients.

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REVIEW OF LITERATURES

Figure:1 LIPID SYNTHESIS, METABOLISM AND TRANSPORT.

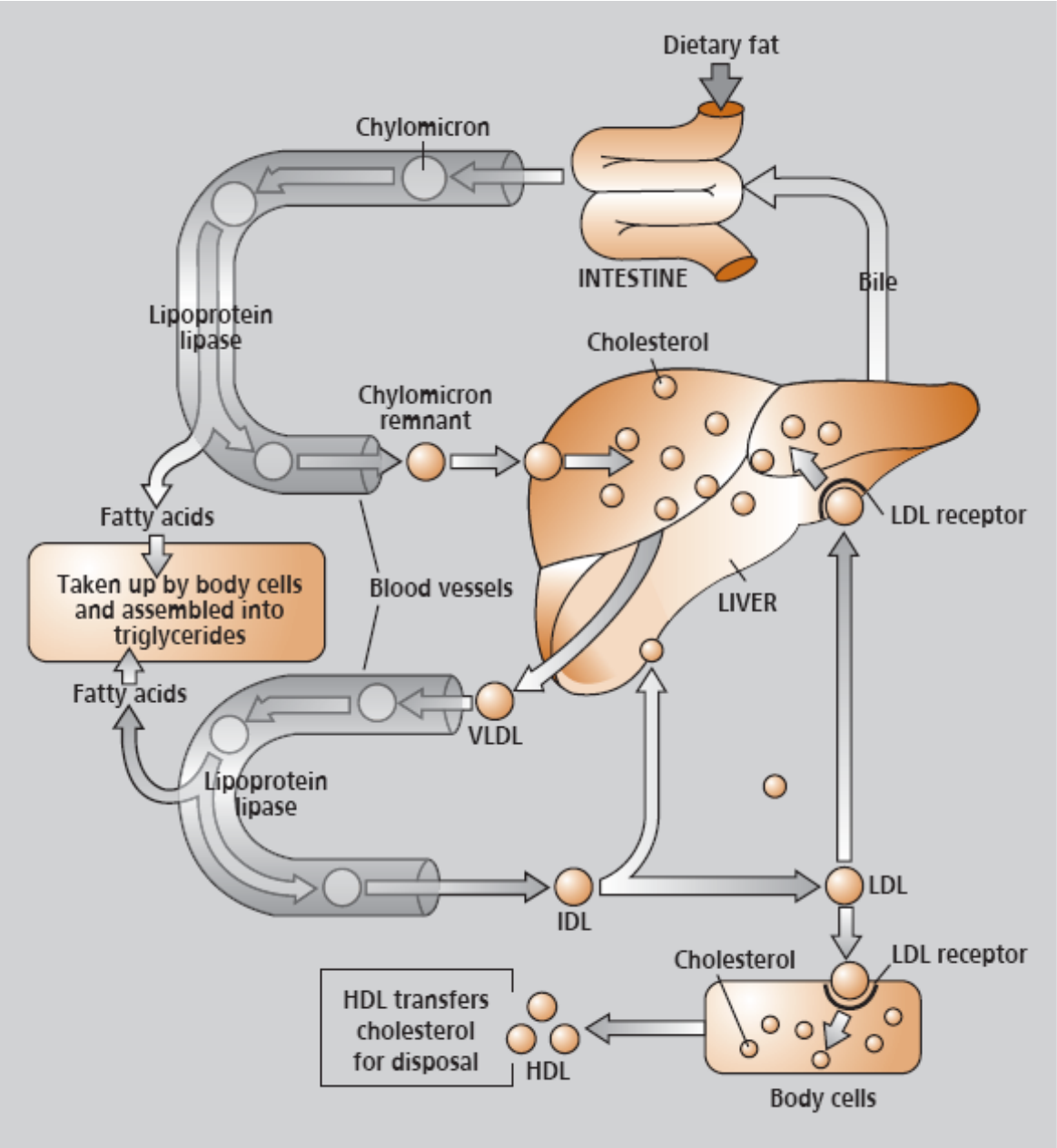


Figure:2 AGE DISTRIBUTION -STUDY GROUP

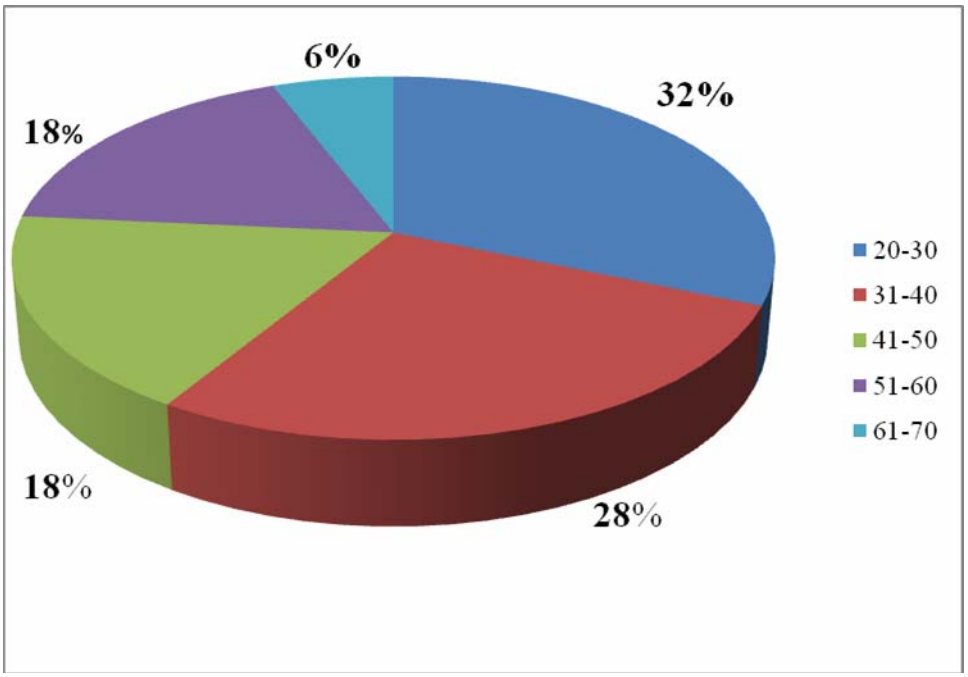


Figure:3

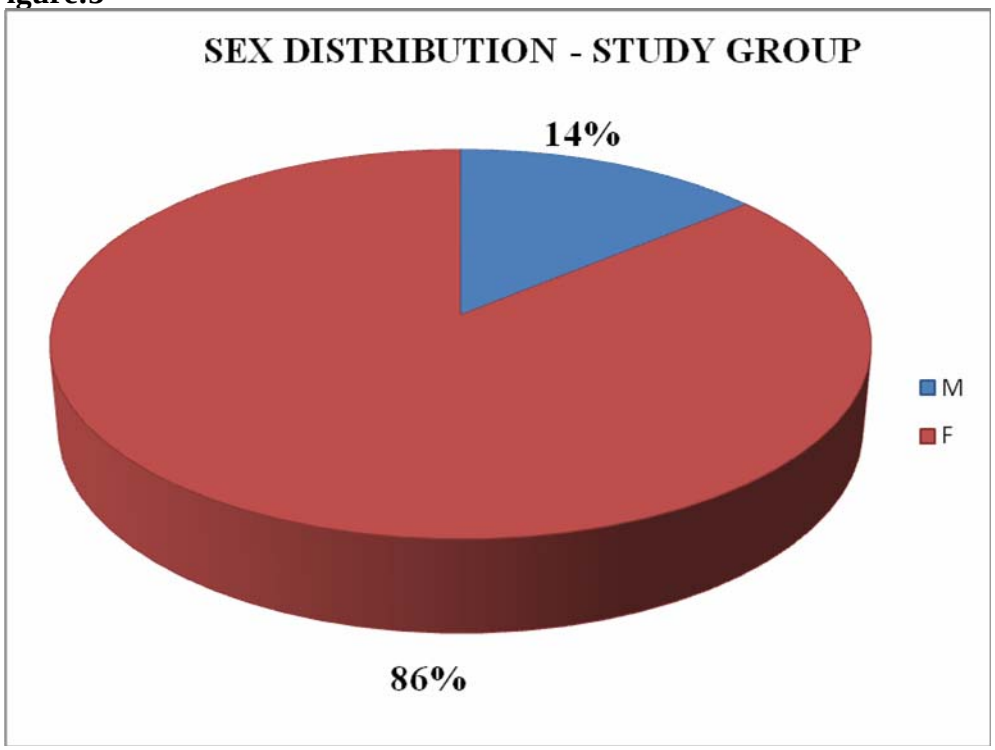


Figure:4 COMPARISION OF LIPID VALUES IN STUDY / CONTROL GROUPS

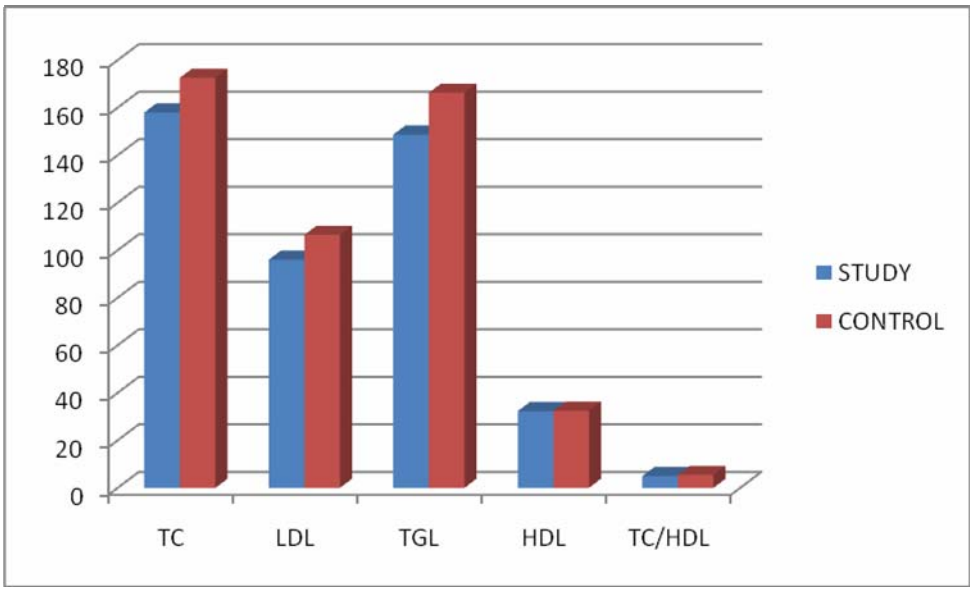


Figure:5 LIPID DISORDER IN STUDY GROUP

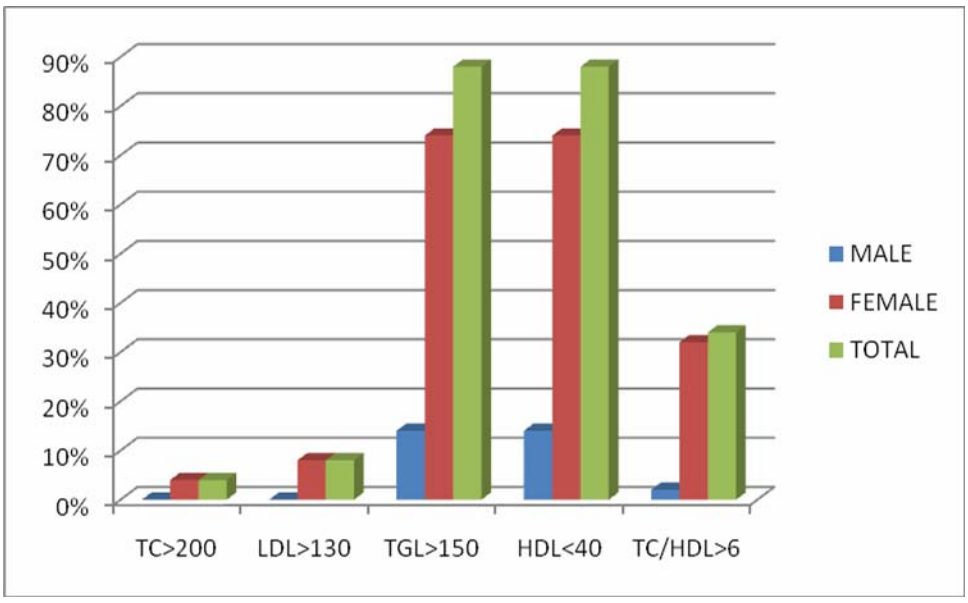


Figure:6 LIPID DISORDER IN CONTROL GROUP

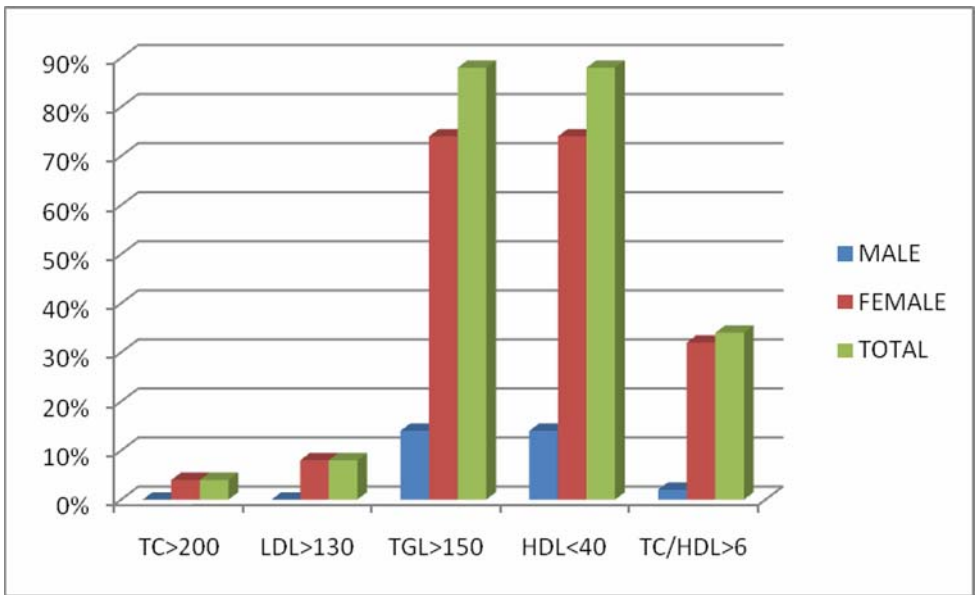


Figure:7 MORNING STIFFNESS DISTRIBUTION IN STUDY GROUP

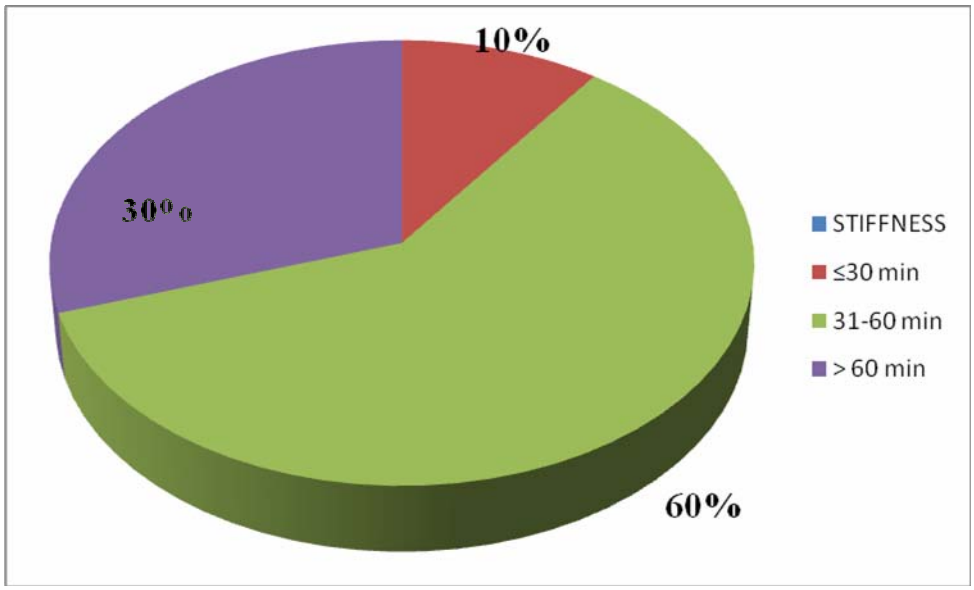


Figure:8

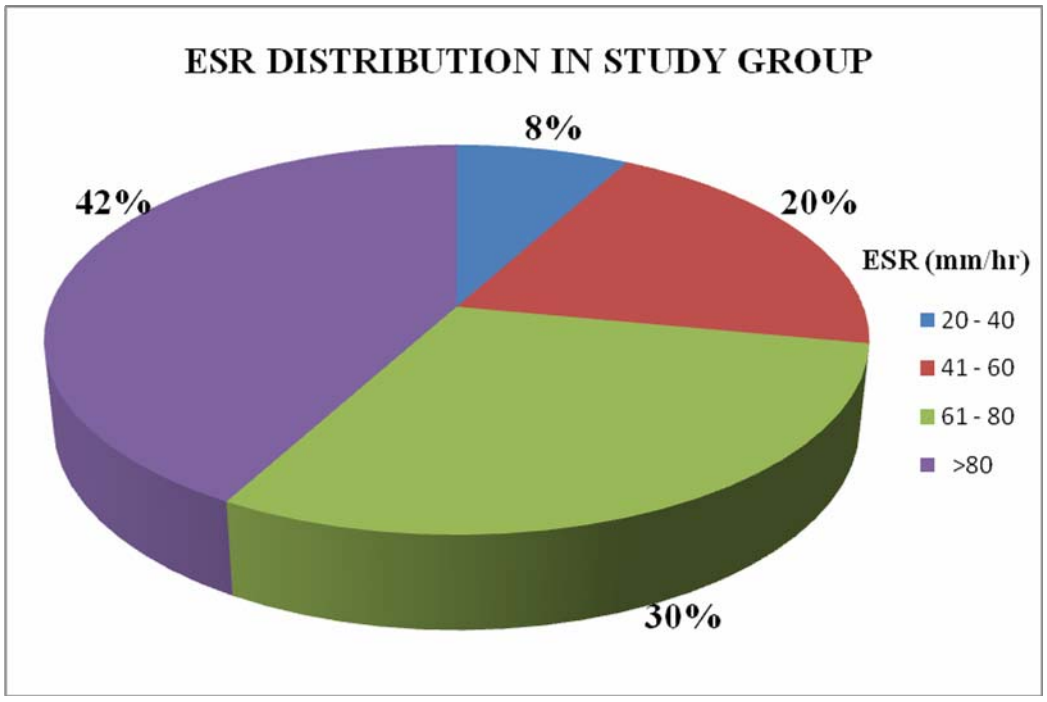


Figure:9

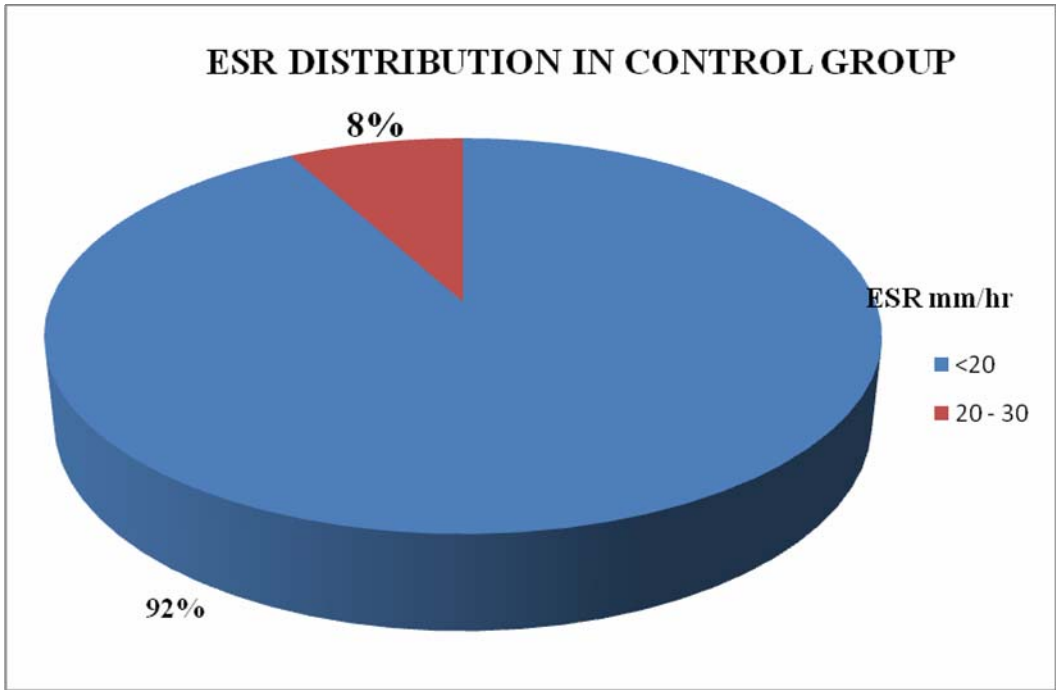


FIGURE:10 CORRELATION BETWEEN LIPID ABNORMALITY AND ESR

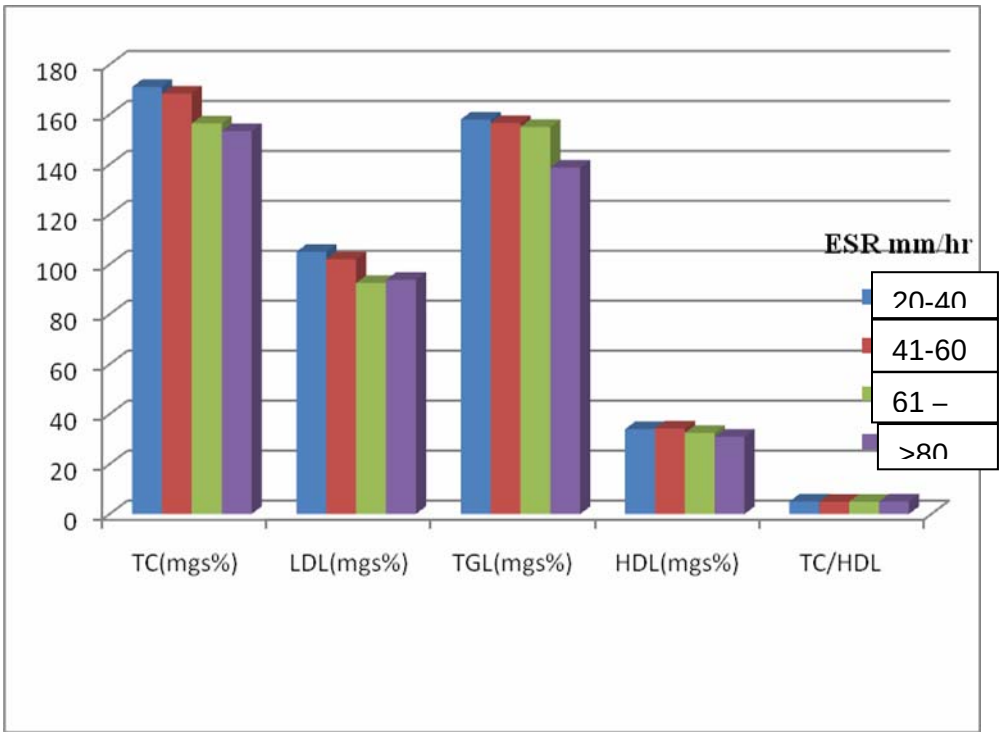


Figure:11 CORRELATION BETWEEN LIPID ABNORMALITY AND EARLY MORNING STIFFNESS

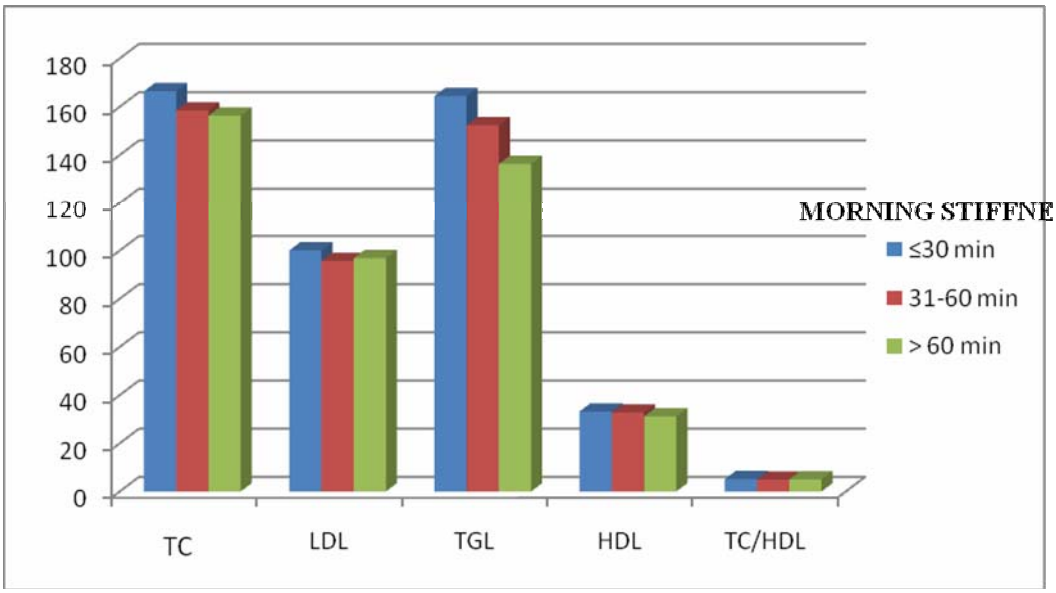
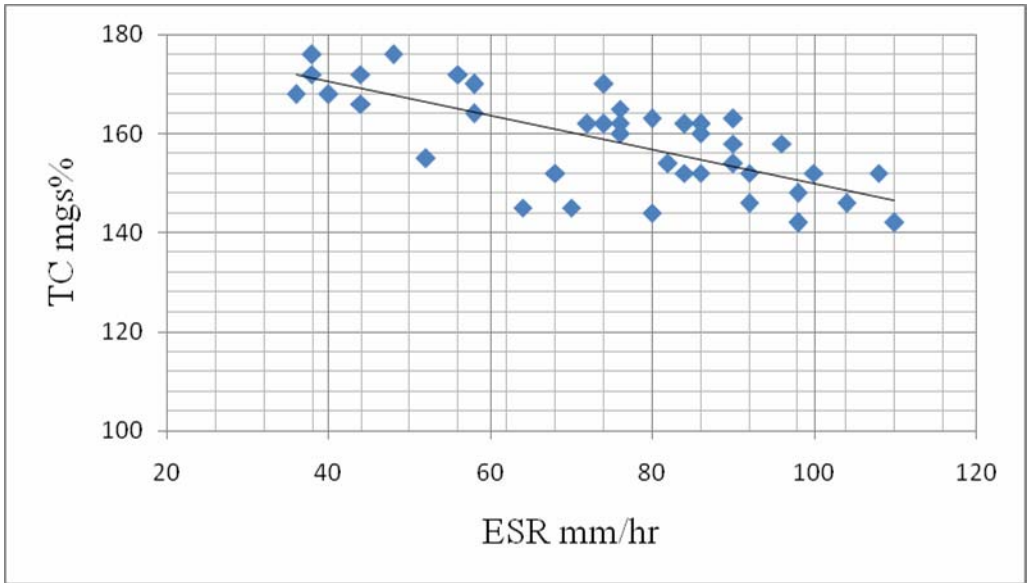
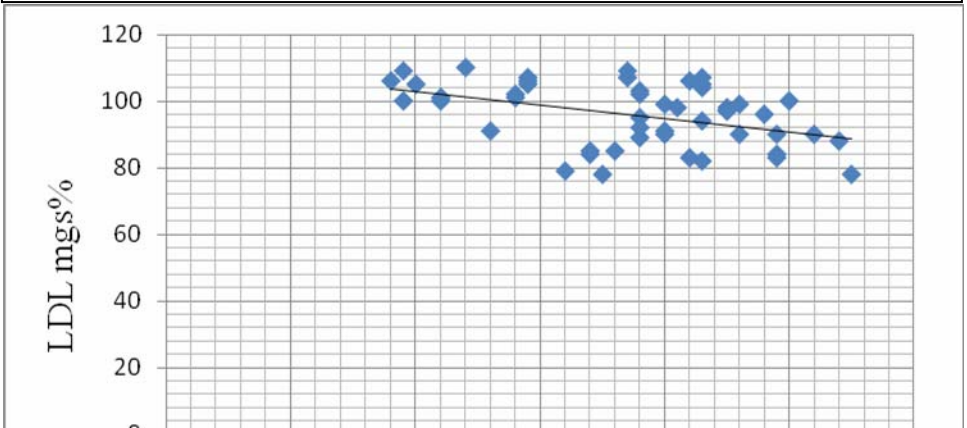


Figure:12 CORRELATION BETWEEN ESR AND TC CHOLESTEROL



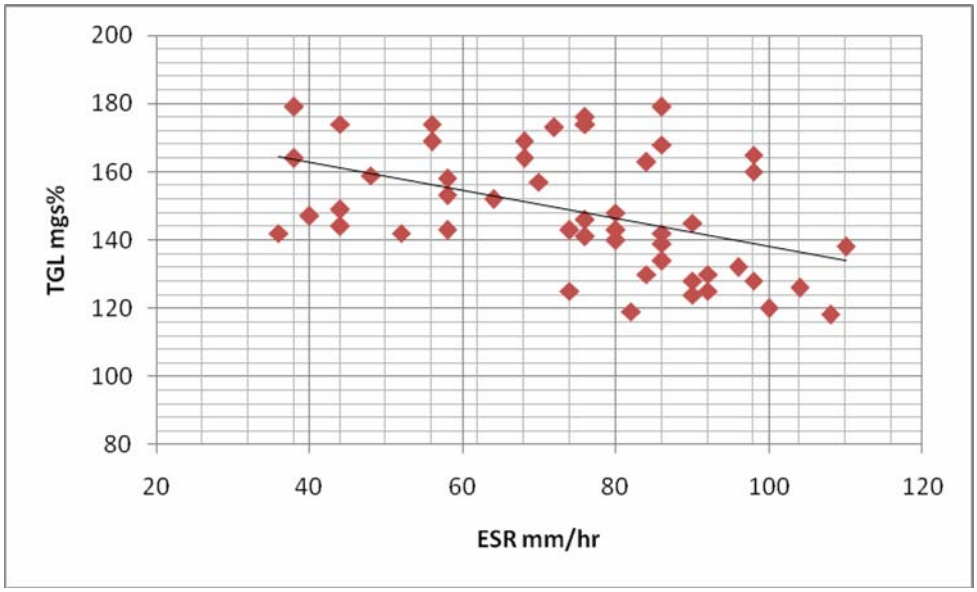
Inverse correlation of ESR with TC(r=-0.701 ,p<0.0001)

Figure:13 CORRELATION BETWEEN ESR AND LDL CHOLESTEROL



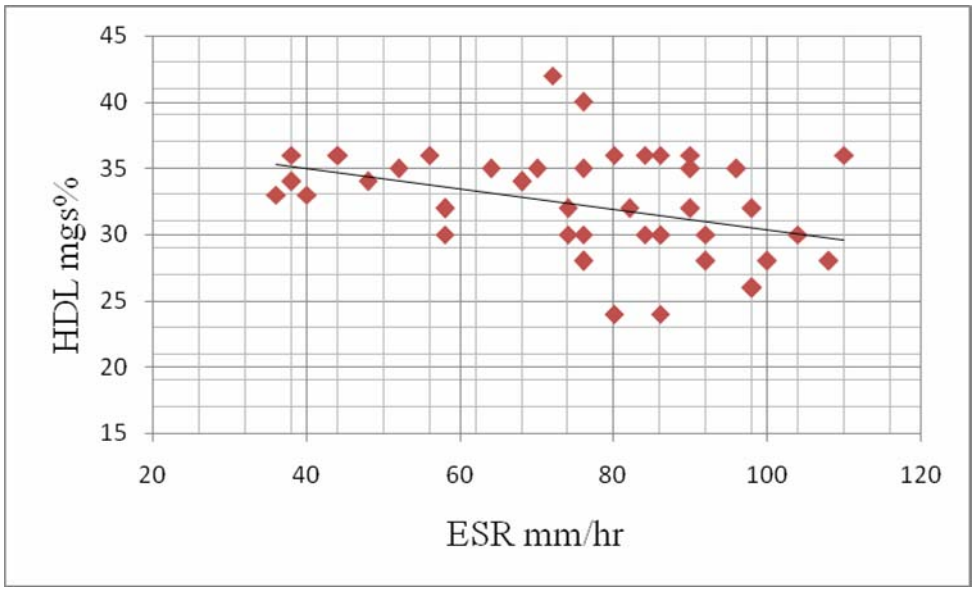
Inverse correlation of ESR with LDL-c (r= -0.436 , p=0.0015)

Figure:14 CORRELATION BETWEEN ESR AND TGL CHOLESTEROL



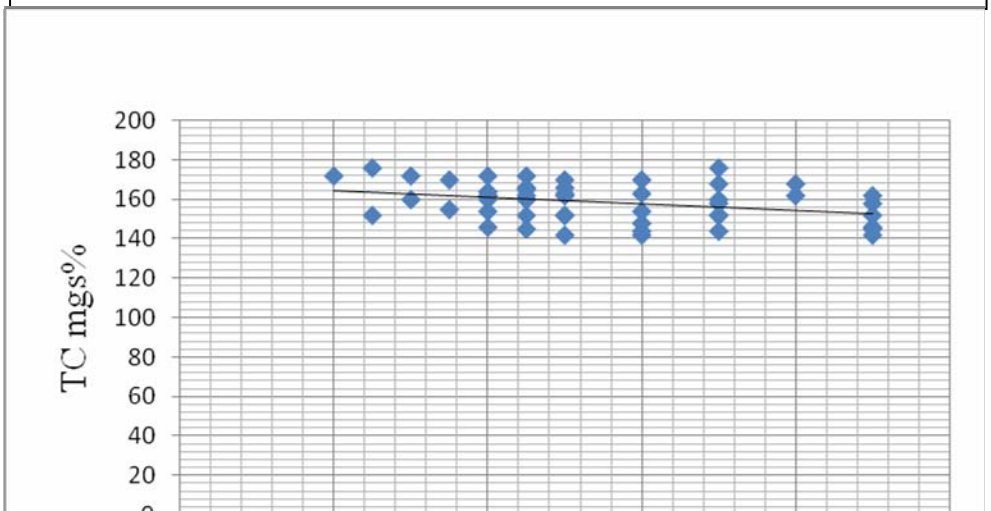
Inverse correlation of ESR with TGL (r= -0.454 ,p= 0.0009)

Figure:15 CORRELATION BETWEEN ESR AND HDL CHOLESTEROL



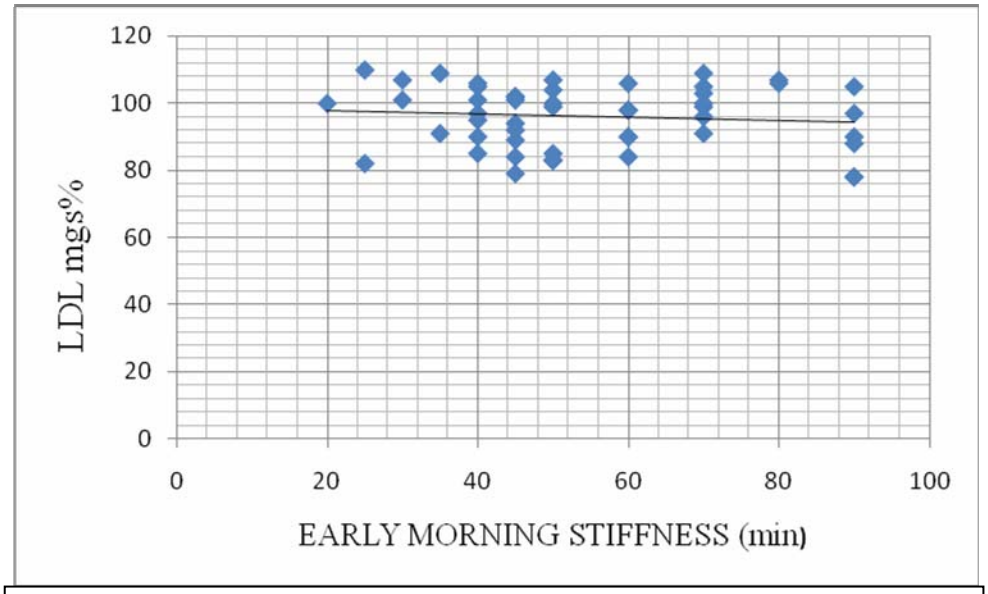
Inverse correlation of ESR with HDL (r= -0.388 ,p= 0.0054)

MORNING STIFFNESS



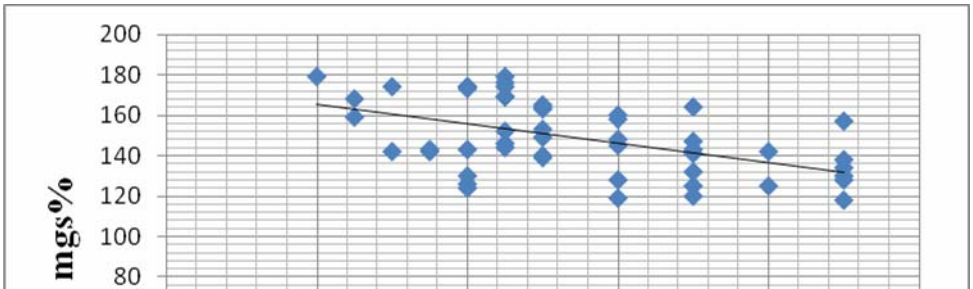
Inverse correlation of TC with Morning stiffness (**r= -0.337, p= 0.0166**)

Figure:17 CORRELATION BETWEEN LDL AND MORNING STIFFNESS



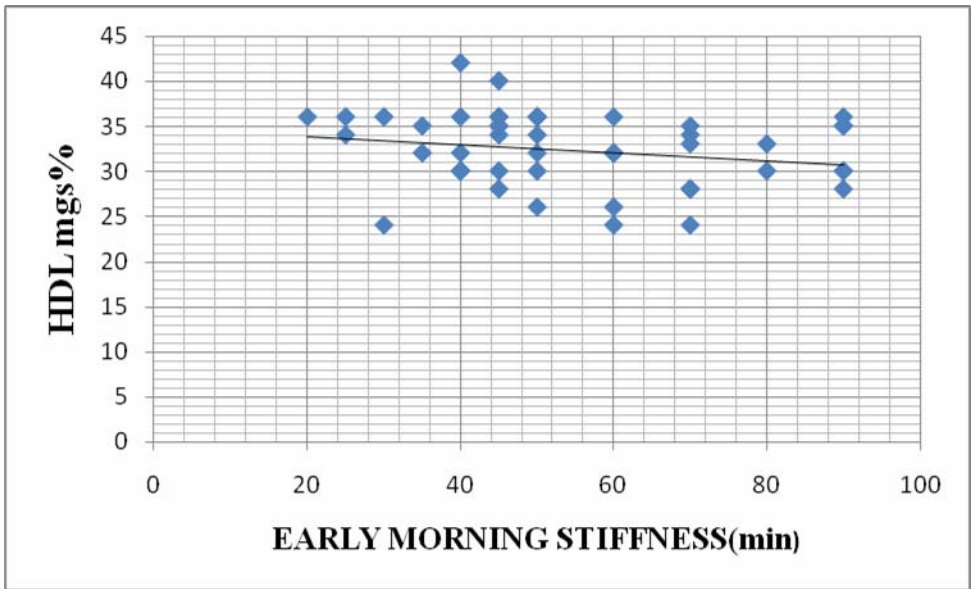
Inverse correlation of LDL with Morning stiffness (**r= -0.103 , p=**

Figure:18 CORRELATION BETWEEN TGL AND MORNING STIFFNESS



Inverse correlation of TGL with Morning stiffness (**r= -0.509 , p=0.0002**)

Figure:19 CORRELATION BETWEEN HDL AND MORNING STIFFNESS



Inverse correlation of HDL with Morning stiffness (**r= -0.211 ,**

MASTER CHART:STUDY GROUP

No	Name	Age	Sex	Rcc.No	TC mgs%	LDL mgs%	TGL mgs%	HDL mgs%	TC/HDL	ESR mm/hr	Morning stiffness in minutes
1	Rani		F	48695	162	104	139	30	5.4	86	50
2	Janaki	53	F	2094	154	98	119	32	4.8	82	60
3	Saroja	55	F	43227	146	90	130	30	4.9	92	90
4	Prema	53	F	45485	176	110	159	34	5.18	48	25
5	Sarada	60	F	49447	163	98	145	36	4.5	90	60
6	Ganesh	27	M	49838	160	103	141	28	5.7	76	70
7	Paulraj	52	M	47554	168	105	147	33	5.1	40	70
8	Amuda	37	F	43998	162	107	125	30	5.4	74	80
9	Saraswathi	45	F	47730	145	78	157	35	4.1	70	90
10	uma	35	F	49229	152	83	163	36	4.2	84	50
11	Vijaya	37	F	40896	172	100	179	36	4.7	38	20
12	Mohana	55	F	50256	172	102	169	36	4.7	56	45
13	Gandhimathi	37	F	43217	152	99	125	28	5.4	92	70
14	Selvanayaki	44	F	50263	170	107	153	32	5.3	58	50
15	Kasthuri	36	F	45010	152	84	169	34	4.5	68	45
16	Sarasu	25	F	47848	158	97	128	35	4.5	90	90
17	Gurunath	67	M	44472	160	94	179	30	5.3	86	45
18	Priya	35	F	49696	144	91	143	24	6	80	70
19	Rajeswari	37	F	49033	166	100	149	36	4.6	44	50
20	Anjali	25	F	46986	142	84	160	26	5.6	98	60
21	Shanthi	50	F	44823	162	105	134	30	5.4	86	90
22	Krishnaveni	28	F	35793	154	97	124	32	4.8	90	40
23	Vimala	30	F	34648	146	90	126	30	4.9	104	40
24	Thilaga	24	F	40648	176	109	164	34	5.17	38	70

SNo	Name	Age	Sex	Rcc.No	TC mgs%	LDL mgs%	TGL mgs%	HDL mgs%	TC/HDL	ESR mm/hr	Morning stiffness in minutes
25	Jayaselan	48	M	49966	163	99	140	36	4.5	80	50
26	Das	49	M	49811	160	102	146	28	5.7	76	45
27	Elcy	44	F	49212	168	106	142	33	5.1	36	80
28	Gunalakshmi	30	F	40682	162	106	130	30	5.4	84	40
29	Munuswamy	23	M	48860	145	79	152	35	4.1	64	45
30	Sivagami	32	F	50016	152	82	168	36	4.2	86	25
31	Rajinisha	35	F	47304	172	101	174	36	4.8	44	30
32	Jamuna	27	F	49698	172	101	174	36	4.8	56	40
33	Indra	50	F	48964	152	100	120	28	5.4	100	70
34	Malliga	45	F	46184	170	106	158	32	5.3	58	60
35	Gowri	30	F	47773	152	85	164	34	4.5	68	50
36	Allice	27	F	50260	158	96	132	35	4.5	96	70
37	Javid	65	M	50067	160	95	174	30	5.3	76	40
38	Vasantha	37	F	39874	144	90	148	24	6	80	60
39	Kanniamal	35	F	23242	166	101	144	36	4.6	44	45
40	Kamala	27	F	23350	142	83	165	26	5.5	98	50
41	Ponnamal	35	F	45611	142	78	138	36	3.9	110	90
42	Mumtaj	40	F	49999	155	91	142	35	4.4	52	35
43	Jayalakshmi	25	F	46140	165	89	176	40	4.1	76	45
44	Kalavathi	20	F	48402	148	90	128	32	4.6	98	60
45	Komathi	70	F	48831	164	105	143	30	5.5	58	40
46	Subbamal	56	F	29419	170	109	143	32	5.3	74	35
47	Geethabai	45	F	45132	152	88	118	28	5.4	108	90
48	Javeena	58	F	49669	162	85	173	42	3.9	72	40
49	Kuppamal	38	F	46147	162	92	174	35	4.6	76	45
50	Chokamal	30	F	45202	160	107	142	24	6.6	86	30

MASRER CHART:CONTROL GROUP

SNO	Name	Age	Sex	OUT PATIENT:.No	TC mgs%	LDL mgs%	TGL mgs%	HDL mgs%	TC/HDL	ESR (mm/hr)
1	Sangeetha	50	F	51553	154	89	175	30	5.1	6
2	malathy	54	F	58223	168	97	173	36	4.7	4
3	Rajeswari	54	F	52980	188	122	169	32	5.9	20
4	Parimala	53	F	52949	196	130	179	30	6.5	22
5	kaliammal	60	F	52746	142	83	183	22	6.4	12
6	kumar	28	M	53640	172	104	169	34	5.1	14
7	sundar	51	M	58431	182	114	177	32	5.7	16
8	Rada	39	F	58446	174	106	154	37	4.7	14
9	Nagalakshmi	44	F	58513	176	106	167	36	4.9	12
10	Venila	34	F	58532	182	122	167	26	7	16
11	Kanchana	37	F	58536	170	107	171	28	6.1	10
12	Rajina bee	54	F	58137	192	126	167	32	6	20
13	Ramani	37	F	58242	152	91	155	30	5.1	8
14	Uma	45	F	58810	184	129	141	26	7.1	6
15	Saroja	35	F	57154	182	111	169	37	4.9	4
16	Saveetha	27	F	57387	184	109	159	43	4.3	18
17	Narasiman	65	M	58983	174	106	173	33	5.3	16
18	Valarmathi	35	F	59086	146	74	159	40	3.6	12
19	Padma	36	F	59387	208	139	175	34	6.1	22
20	Rosemary	26	F	59537	168	106	157	30	5.6	14
21	Mangai	51	F	56767	154	89	172	30	5.1	12
22	Geetha	29	F	58914	168	96	178	36	4.7	10
23	Shanthi	29	F	59148	188	123	164	32	5.9	16
24	Saraswathi	23	F	59161	196	129	184	30	6.5	18

SNO	Name	Age	Sex	OUT PATIENT:No	TC mgs%	LDL mgs%	TGL mgs%	HDL mgs%	TC/HDL	ESR (mm/hr)
25	Younis	48	M	59581	142	84	178	22	6.4	6
26	Murugan	47	M	59302	172	103	174	34	5.1	10
27	Mayavathi	46	F	59860	182	115	172	32	5.7	12
28	Meerajothi	30	F	58081	174	105	160	37	4.7	14
29	Jayaram	25	M	59549	176	107	162	36	4.9	12
30	Rosy	30	F	60179	182	121	172	26	7	14
31	Sankunthala	35	F	60228	170	108	166	28	6.1	10
32	Arokiamary	28	F	60260	192	125	172	32	6	10
33	Hemalatha	51	F	59090	152	92	150	30	5.1	8
34	Alamelu	45	F	60293	184	128	146	26	7.1	16
35	Kantha	30	F	60722	182	112	164	37	4.9	18
36	Padma	28	F	60524	184	108	164	43	4.2	8
37	mani	64	M	55690	174	107	168	33	5.3	6
38	Suguna	37	F	61803	146	73	164	40	3.6	4
39	Ragavamal	35	F	62004	208	140	170	34	6.1	18
40	Salima	28	F	62115	168	105	162	30	5.6	8
41	Parvathy	34	F	62156	148	71	164	44	3.4	10
42	Kousalya	40	F	60375	184	120	180	28	6.6	12
43	Mohana	37	F	60281	152	89	182	26	5.8	8
44	Antonyamal	35	F	60455	164	87	174	42	3.9	8
45	Venkatamal	29	F	62180	198	141	132	30	6.6	12
46	Chinnaponu	33	F	62388	170	109	130	35	4.8	10
47	Jothy	40	F	62333	174	107	174	32	5.4	14
48	Valli	27	F	60555	166	109	144	28	5.9	6
49	Geetha	70	F	62432	154	91	192	24	6.4	8
50	Shantha	38	F	62543	132	61	162	38	3.5	14